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Evaluation of Progesterone (17-α hydroxyprogesterone caproate) Utilization, Adherence, and Outcomes in Women with a High-risk Pregnancy

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Evaluation of Progesterone (17-α hydroxyprogesterone caproate) Utilization, Adherence and Outcomes in Women with a High-risk Pregnancy

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Abstract

Evaluation of Progesterone (17-α hydroxyprogesterone caproate) Utilization, Adherence, and Outcomes in Women with a High-risk Pregnancy

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The aims of this study were to investigate the utilization, adherence, and effectiveness of 17- α hydroxyprogesterone caproate (17-OHPC) for patients with a history of preterm birth (PTB). A retrospective cohort study was conducted using 2012-2017 data from the Decision Recourses Group (DRG) database. The first diagnosis of high-risk pregnancy was the index date. A 6-month pre-index period was applied, and the patients were followed to delivery. Descriptive statistics, chi-square tests, and logistic regressions were used for data analysis.

A total of 23,911 patients met criteria, with 2,051 (8.58%) having ≥ 1 claim for 17-OHPC. Patients with commercial insurance were more likely to use 17-OHPC compared with Medicaid patients ($p<0.0001$); and patients residing in the Southwest were more likely to use 17-OHPC compared with patients residing in other areas of the U.S. ($p<0.0001$). Of the 2,051

women prescribed 17-OHPC, 407 (19.84%) were adherent using our baseline definition of adherence. No association was found between patients' adherence rates and their demographic or clinical characteristics.

Older patients aged 30-35 and aged ≥35 were 28% (OR=0.72, 95% CI=0.64-0.79) and 34% (OR=0.66, 95% CI=0.59-0.74) less likely to have PTB, respectively, than patients aged <25; patients residing in the Southeast area were 12% less likely to have PTB (OR=0.64, 95% CI=0.54-0.75) than Northeast patients; patients with hypertension were 15% (OR=1.15, 95% CI=1.02-1.29) more likely to have PTB, than patients without hypertension; patients with a CCI score of 1, 2, or ≥3 were 10% (OR=1.10, 95% CI=1.01-1.20), 26% (OR=1.26, 95% CI=1.14-1.41), and 35% (OR=1.35, 95% CI=1.17-1.56) more likely to have PTB, respectively, than patients with a CCI score of 0. After controlling for covariates, the incidence of PTB was not found to be associated with utilization of (p=0.44) or adherence to 17-OHPC (p=0.14). The use of 17-OHPC was not associated with the incidence of diabetes (p=0.21). However, the use of 17-OHPC was shown to be associated with a lower incidence of hypertension (p=0.01).

In conclusion, 17-OHPC use was low (<10%), adherence was low (<20%), and there was no evidence of effectiveness.

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LIST OF ABBREVIATIONS

Acronym	Definition
ACOG	American College of Obstetricians and Gynecologists
BMI	Body-Mass Index
CCI	Charlson Comorbidity Index
CPT	Current Procedural Terminology
DRG	Decision Resources Group
EAPM	European Association of Perinatal Medicine
EMR	Electronic Medical Records
fFN	Fetal Fibronectin
FDA	U.S. Food and Drug Administration
GDM	Gestational Diabetes Mellitus
GHT	Gestational Hypertension
ICD	International Classification of Diseases
IOM	Institute of Medicine
IVF	In Vitro Fertilization
MCO	Managed Care Organizations
MCP-1	Monocyte Chemoattractant Protein-1
MMCO	Medicaid Managed Care Organizations
NICHD	National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network
PA	Prior Authorization
PAMG-1	Placental Alpha Microglobulin-1
PDC	Proportion of Days Covered
PPROM	Preterm Premature Rupture of Membranes
PR-A	Progesterone receptor A
PR-B	Progesterone receptor B
PROLONG	Progestin's Role in Optimizing Neonatal Gestation
PTB	Preterm Birth
RCT	Randomized Control Trial
SMFM	The Society for Maternal-Fetal Medicine
SPTB	Spontaneous Preterm Birth
WHO	World Health Organization
17-OHPC	17α- Hydroxyprogesterone Caproate

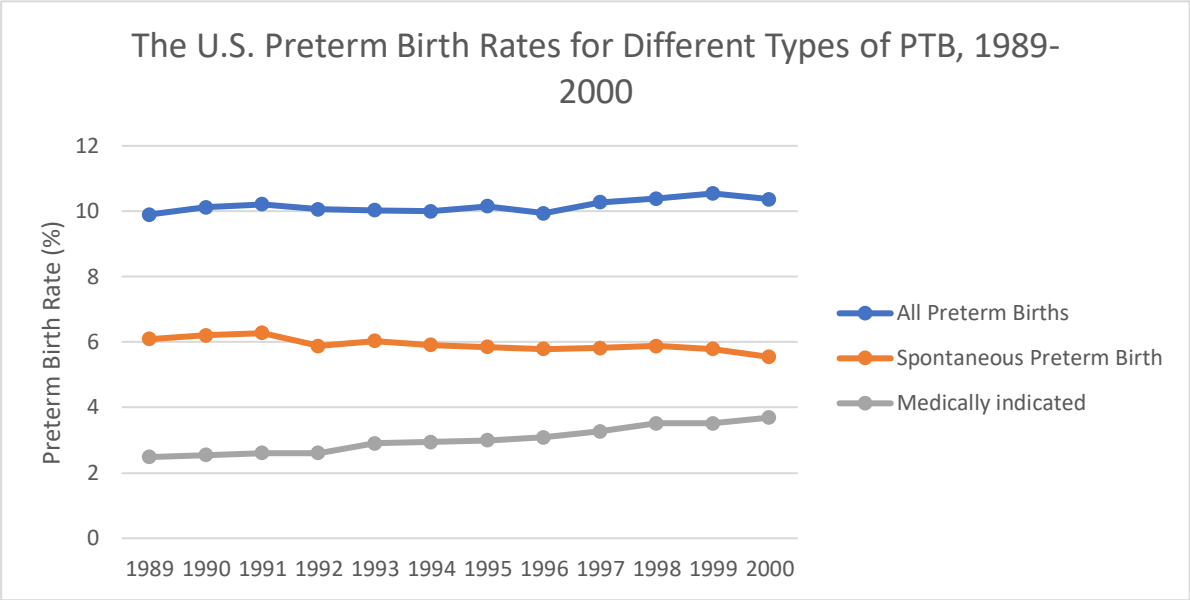
Chapter 1 Introduction

1.1 Definition and Classification

Preterm birth (PTB) is also known as premature birth. The World Health Organization (WHO) defines PTB as "babies born alive before 37 weeks of pregnancy are completed," based on gestational age, which is a measure of pregnancy age.[1] It is usually estimated by menstrual history, clinical examination of uterus size, and ultrasound biometric measurement.[2] Gestational age plays an essential role in predicting prenatal development events and estimating the date of delivery.[3] According to gestational age, PTB can be stratified into three sub-types. When the gestational age is less than 28 weeks, it is treated as 'extremely preterm.' 'Very preterm' occurs between 28 and 32 weeks. If babies are born between 32 and 37 weeks, it is considered a 'moderate to late preterm' birth.[1] In addition, early term, full term, late term, and post term take place between 37 0/7 and 38 6/7 weeks, between 39 0/7 and 40 6/7weeks, the 41st week, and after 42 weeks, respectively.[4]

PTB can also be categorized by the obstetric etiological precursors, in which PTB includes spontaneous preterm birth (SPTB) and medically indicated PTB.[5,6] Medically indicated PTB refers to delivery for maternal or fetal indications, which accounts for one-third of PTBs,[7,8] and occurs because of physicians' interventions—either inducing the labor or performing a pre-labor cesarean delivery.[6,9] SPTB is the most common type of PTB (66%), occurring when a woman goes into labor with intact membranes (40-45%) or preterm premature rupture of membranes (PPROM) (25-30%).[6-8,10] The rates of different types of PTB are shown in Figure 1.1.

Figure 1. 1 U.S. Preterm Birth Rates for Different Types of PTB from 1989 to 2000



Source: Ananth CV, Joseph KS, Oyelese Y, et al. Trends in preterm birth and perinatal mortality among singletons: United States, 1989 through 2000. *Obstetrics & Gynecology* 2005;105(5):1084-1091.[11]

Recurrent PTB is another subgroup of PTB based on the previous number of PTBs. It refers to "more than one delivery before 37 gestational weeks occurring for the same woman," which can be either recurrent indicated PTB or recurrent SPTB.[12] A summary of different types of PTB and standards of classification are listed in Table 1.1.

Table 1. 1 Classification of Preterm Birth

Classification Standards	PTB Types	Operational Definitions
Categorized by gestational age	Extreme preterm	Gestational age < 28 weeks
	Very preterm	Gestational age ≥ 28 and < 32 weeks
	Moderate to late preterm	Gestational age ≥ 32 and < 37 weeks
Categorized by obstetric etiological precursors	Medically indicated PTB	Occurs because of physicians' interventions
	Spontaneous PTB	Occurs spontaneously (no intervention)
Categorized by number of prior PTBs	Recurrent PTB	More than one PTB occurring for the same woman

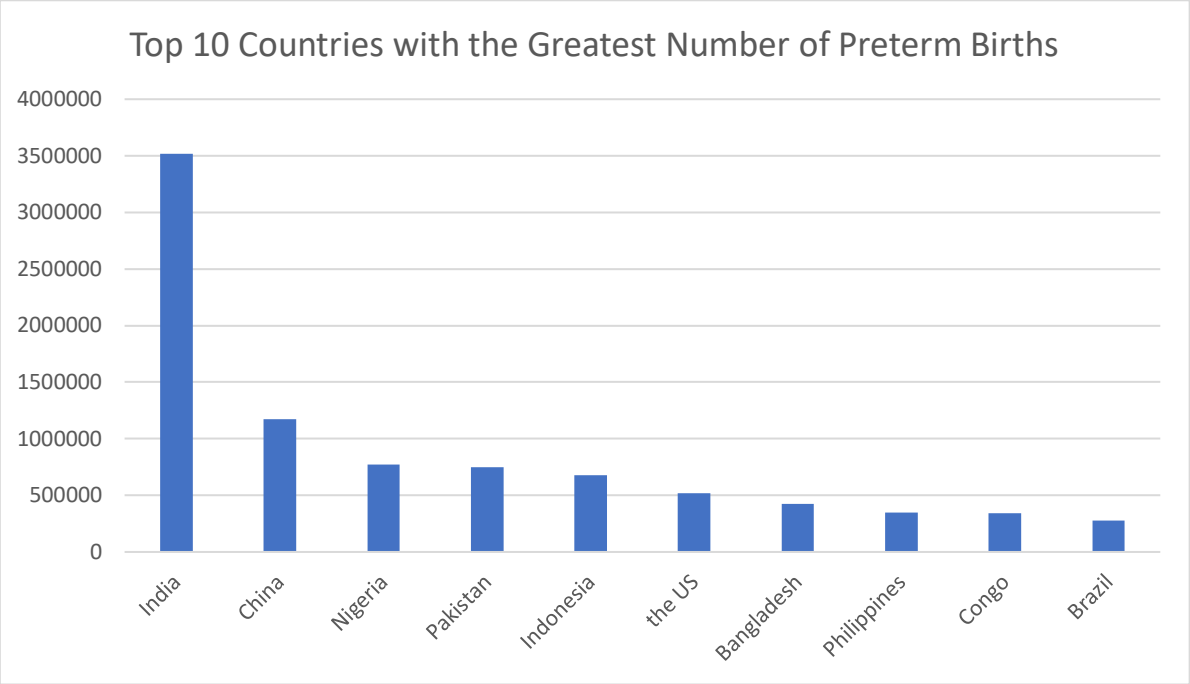
1.2 Epidemiology of Preterm Birth

PTB is the most common reason for neonatal mortality and morbidity worldwide, with

approximately 15 million preterm infants born each year.[1] Globally, the leading cause of death of children under 5 years and long-term disability is PTB complications, which result in approximately 1 million children dying every year.[13] Three-fourths of perinatal mortality and over 50% of long-term morbidity are due to PTB.[8] The survival rate of preterm infants born at 22 weeks is about 6%, and rises to 72% at 25 weeks.[14] In addition to low survival rate, since some important organs of preterm infants (e.g., brain, lungs, and liver) are still in the process of developing, these infants face a high risk of multiple health problems, such as cerebral palsy, delays in development, sensory deficits, hearing problems, and respiratory illnesses.[15,16]

Even though PTB is a global issue, its prevalence varies across the world, ranging from 5% to 18% across 184 countries.[1] PTB occurring in Africa and South Asia accounts for more than two-thirds of global PTB, with estimated PTB rates of 11.6% and 11.4%, respectively.[1,15] This problem is more common in low-income countries. The three countries with the highest rates of PTB per 100 live births are Malawi (18.1%), Comoros (16.7%) and Congo (16.7%) (2018).[1,17] Among countries with the greatest number of PTBs, India, China, and Nigeria are ranked in the top three (2018).[1] Compared to developing countries, the incidence rates of PTB for developed countries are relative low. Estimated PTB rates are reported to be 5-9 % for European countries, and approximately 6% for Oceanic countries (2008).[8,15]

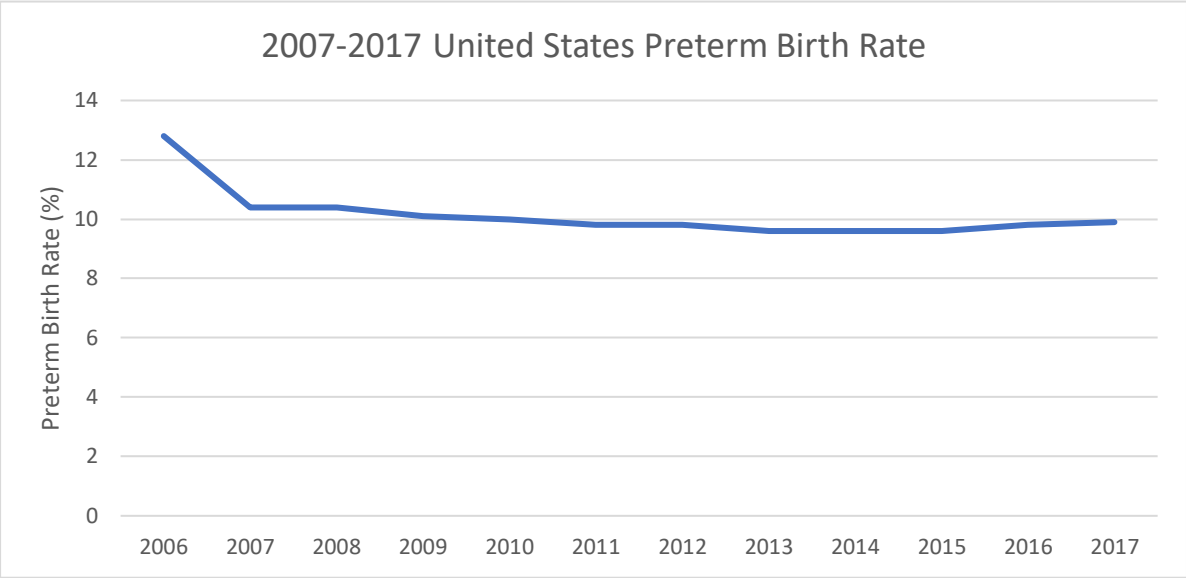
Figure 1. 2 Top 10 Countries with the Greatest Number of Preterm Births



Source: WHO. Preterm birth: Key facts. 2018; http://www.who.int/en/news-room/fact-sheets/detail/preterm-birth[1]

The United States has the highest PTB numbers among developed countries, and ranks 6th of countries with the greatest number of PTBs.[1] It is also the only developed country on the top 10 list (See Figure 1.2).[18] In the late 20th century, the PTB rate of the U.S. showed a steady rising tendency, increasing from 9.5% in 1981 to the peak of 12.8% in 2006.[18-20] Since then, the PTB rate has been declining. However, a recent report published by the March of Dimes, a nonprofit organization concerned with the health of mothers and babies, presented a rise in the U.S. PTB rate from 9.6% in 2015 to 9.9% in 2017, with the highest PTB rate of 13.6% in Mississippi, followed by 12.6% in Louisiana, and 12.0% in Alabama (See Figure 1.3).[21]

Figure 1. 3 United States Preterm Birth Rate, 2007-2017



Source: Adapted from March of Dimes. 2018 Premature Birth Report Card United States. 2018. https://www.marchofdimes.org/materials/PrematureBirthReportCard-United%20States-2018.pdf [21]

1.3 Economic Burden of Preterm Birth

The Institute of Medicine (IOM) (2007) estimated the annual societal cost attributed to PTB in the U.S. as $26 billion ($US 2005).[22] Disability-specific lifetime medical costs, educational costs, and lost productivity costs were taken into consideration for this estimation.[20] Medical costs for each preterm child was estimated to be about ten times greater ($32,325) than that for term children ($3,325) during the first year of life,[22] which is similar to estimates in England and Wales in 2006 ($35,471).[23] The estimates for 'very preterm' and 'extremely preterm' infants were even higher, at $95,760 and $146,847, respectively.[23] Grosse et al. (2017) used private health insurance claims data during 2013 to calculate first-year expenditures for employer-sponsored health plans for preterm born infants. They reported that 7.7% of insured preterm infants accounted for 37% of the $2.0 billion spent on the care of infants, and PTBs cost the included plans an extra $600 million during the infants' first year of life. They also extrapolated the results to the national level, and projected aggregate employer-

sponsored plan expenditures of $6 billion for preterm infants. In addition, the mean expenditures for preterm infants with major birth defects ($226,840) is 3.5 times greater than full-term infants with major birth defects.[24]

Jacob et al. (2017) also compared the health care costs associated with early preterm, late preterm, and full-term birth based on 2011-2012 claims data from a German health insurance company. They found that the average costs of early preterm, late preterm, and full-term infants in the first year after birth were 74,009 EUR, 8,565 EUR, and 1,590 EUR, respectively. Cost differences tended to decrease in the second and third year after birth, though the ambulatory treatment costs did not decrease for early preterm births but decreased for late preterm and full-term births.[25]

In terms of hospitalizations related to PTB, the average length of hospital stays for preterm infants after birth is 13 days, which is approximately eight times longer than the average 1.5 days for term babies.[22] Russell et al. (2007) estimated the cost of hospital admissions for preterm infants in the U.S. accounted for about half of the costs (47%) of all infant hospitalizations and more than one-fourth (27%) of all pediatric stays.[26] According to McLaurin et al.'s study (2009), late preterm infants had 12.6 times higher mean expenditures for the hospitalization than full-term infants.[27] Stephen et al. (2016) used birth data of Australia from 2001 to 2011, finding that the mean costs per hospitalization were $26,800, $9,850, and $4,980 for infants born at 24-27, 28-31, and 39-40 weeks of gestation, respectively.[28] Given the lack of more recent studies on different types of costs related to PTB, new studies are warranted.

The sizable cost differences for preterm infants are mainly due to neonatal intensive

care, infant complication treatment costs, and ongoing healthcare costs.[17,23] According to a study in England and Wales (2009), costs borne during the neonatal period represented 92.0% of the incremental cost per preterm survivor.[23] Simultaneously, in order to take care of the mother and the preterm baby, more family member support is needed, which results in decreased productivity.[17] In the long run, it is possible that families also face the responsibility to care for their disabled children with increased day-care costs and costs for nutrition and alternative therapies.[10,29] The economic effects may also extend to the survivors' possible lower education level, lower income, and increased need for social support.[30]

1.4 Signs and Symptoms

In most cases, preterm labor can be asymptomatic and unexpected. Some warning signs of preterm labor are similar to regular labor, such as uterine contractions every 10 minutes or more often, changes in vaginal discharge (can be an increase in amount, or a change in color), changes in urinary habits (increased frequency or burning sensation), pelvic pressure, low and dull backache, menstrual-like cramps, or abdominal-intestinal cramps with or without diarrhea.[31,32] Some clinical predictors of PTB include initial cervical dilatation of 3cm or more, cervical effacement of 80% or more, vaginal bleeding, and ruptured membranes.[33] Since the initial symptoms and signs are mild and can happen during a normal pregnancy, it is difficult to predict PTB.[33]

1.5 Risk Factors

PTB is a multi-factorial syndrome, which may be driven by multiple mechanisms.[8] No definite causal pathway of PTB has been established, but a number of risk factors have been reported. By identifying risk factors of PTB, healthcare providers may target high-risk pregnant

women and provide corresponding prevention or treatment approaches. Therefore, gathering more insights about risk factors can help to investigate the exact mechanisms of PTB in the future.

Several ways of clustering risk factors were reported by different researchers. Moutquin et al. categorized risk factors by types of PTB, including risk factors of medically induced PTB, PPROM, and SPTB.[5] Alleman grouped them into chronic stresses, acute stressors, and underlying genetic risk.[10] Goldernberg et al. categorized them into maternal risk factors and fetal risk factors. Maternal risk factors include maternal demographic characteristics, pregnancy history, pregnancy characteristics, and biological and genetic markers.[8] This paper mainly focuses on introducing risk factors related to SPTB, despite some risk factors shared by more than one type of PTB.

1.5.1 History of Preterm Birth

Having a history of PTB is one of the strongest risk factors of SPTB. A systematic review and meta-analysis of literature from 1948 to 2017 concluded that the absolute risk of PTB recurrence was 30%.[34] Bloom et al. found the PTB recurrence rate was also related to the number of previous PTBs, with rates of 16%, 41%, and 67% for those with 1, 2, and 3 previous PTBs.[35]

According to studies from different countries, pregnant women with a history of PTB are approximately 2 to 5.7 times more likely to have a subsequent SPTB.[35-40] Mercer et al. reported that compared to women without prior PTB, women with prior PTB had a 2.5-fold increased risk of SPTB for their current gestation.[40] By conducting a retrospective study based on data from five Japanese perinatal centers from 2008 through 2012, Yamashita et al. found

that a previous PTB had a twofold increased risk of SPTB (OR=2.26, 95% CI=1.19-4.30).[37] Based on U.S. data (Missouri), Ananth et al. reported that women who had a SPTB in their first pregnancy were three times more likely to deliver preterm spontaneously during the next pregnancy (OR=3.6, 95% CI=3.2-4.0).[38] Leal et al. also reported similar results using a national population-based sample of Brazilian women (OR=3.74, 95% CI=2.92-4.79).[36] Carlini et al. investigated the risk factors for SPTB in northern Italy, and the results showed that previous PTB had a significant association with PTB (OR=5.7, 95% CI=2.5-12.9).[39] Bloom et al. found women who delivered a singleton before 35 weeks were 5.6 times more likely to have recurrent PTB; the odds ratio for recurrent PTB with intact membranes was 7.9, and 5.5 with ruptured membranes.[35] Prior early PTB (or very PTB) showed a more extreme increased risk for recurrent PTB. Moreover, there is research showing that gestational age of women with a second PTB is similar to that of their first pregnancy.[38]

1.5.2 Black Race

Generally, PTB rates are lower among east Asian, White, and Hispanic women, but higher in Black women, with the PTB rate for Black women ranging from 16-18%, compared to 5-9% for White women.[8] U.S. birth data for 2017 shows that the PTB rates were 13.93% for Black women, 8.53% for Asian women, 9.05% for White women, 11.86% for American Indian or Alaska Native women, and 9.62% for Hispanic women.[41] There have been many studies reporting that Black, African-American, or Afro-Caribbean women have a higher risk for recurrent PTB than other races, though the differences have not been adequately explained despite accounting for disparities in prenatal treatment, history of pregnancy, and other behavioral factors.[8,42-45] Kistna et al. used the Missouri Department of Health's maternally

linked database and found that Black women were approximate 4 times more likely to have recurrent PTB and earlier gestations than White women.[42] Another cohort study using data from Georgia reported that African-American women were at higher risk of recurrent PTB than Caucasian women (13.4% vs 8.2%).[43] TNF-2 and SERPINH1 are two candidate genes accounting for PTB in African-American women.[18] However, in spite of similar carrier frequencies for the allele, African-American women (OR=2.5) still had a higher risk of SPTB than Caucasians (OR=1.6).[46]

1.5.3 Short Cervical Length

Cervical length refers to the length of the lower end of the uterus. Typically, the shorter the cervical length, the greater risk women face for SPTB.[8,12] Compared to a cervix of normal length, it is more difficult for a short cervix to remain closed during pregnancy, which results in cervical insufficiency, defined as "the inability of uterine cervix to retain a pregnancy in the absence of contractions or labour."[12,47] The normal length of a cervix in a non-pregnant woman is 40mm to 50mm. But during pregnancy, the cervix will gradually soften, shorten, become thinner, and finally open when the body is ready to give birth.[48] The normal cervical length is 40-45mm at 16 to 20 weeks, 35-40mm at 24-28 weeks, and 30-35mm at 32-36 weeks.[49] There is no consensus on the cut-off point of defining a sonographic short cervix.[50] The definition of "short" cervix varies from 15mm to 30mm across different studies; however, clinically, 25mm is usually used to define a "short" cervix.[47,50-54] In 1996, Iams et al. proposed that a shorter cervix may indicate a greater risk of SPTB. The results showed the relative risks of SPTB increased as the cervix length decreased (RRs= 3.79 for 30 mm, 6.19 for 26mm, 9.49 for 22mm and 13.99 for 13mm). [54]

1.5.4 Low Maternal Body-Mass Index (BMI)

Low pregnancy BMI and low pre-pregnancy BMI can both lead to an increased risk of SPTB; moreover, low maternal BMI is also related to low birth weight ($r=0.157$, $p=0.041$).[55] In a meta-analysis examining the relationship between maternal weight and the risk of PTB, the results showed the risk of SPTB was increased in underweight (BMI ≤ 20) women (adjusted RR=1.32, 95% CI=1.10-1.57).[56] Low BMI can be an indicator of poor nutritional status of pregnant women. Thin women often consume less vitamins and minerals, resulting in low serum iron, folate, or zinc levels.[57] Malnutrition increases a woman's vulnerability to maternal infection and decreased blood flow.[58]

1.5.5 Multiple Gestation

Multiple gestation is one of the risk factors for PTB. Multifetal gestations only account for 2-3% of infants, but they are related to 10-20% of all PTBs.[8] Nearly 50-60% of women with a twin gestation gave birth before the 37th week of gestation.[6,59] Multiple gestation has an influence on both indicated and spontaneous PTB, with SPTB accounting for 70% of PTB in multiple births.[60] As for the association between multiple gestation and recurrent PTB, there is no agreement if multiple gestation results in a higher risk of recurrent PTB. Menard et al. claimed that PTB in twin gestations was significantly associated with increased risk of PTB in a subsequent singleton pregnancy, with 19.6% of women who delivered preterm twins delivering preterm (before 37 weeks of gestation) in a subsequent singleton pregnancy (RR=2.87, 95% CI=1.02-8.09), and with 42% of subsequent singleton pregnancies delivered preterm for women who delivered twins before 30 weeks of gestation (RR=6.11, 95% CI=2.07-18.02).[61] In contrast, Bloom et al. reported a significant higher risk for recurrent PTB among

women who previously delivered a singleton preterm (OR=5.6, 95% CI=4.5-7.0), but not for those who previously delivered twins preterm (OR=1.9, 95% CI=0.48-8.14).[35]

1.5.6 Other Risk Factors

In addition to the above-mentioned risk factors, there are other factors associated with a higher risk of PTB. Prior cervical surgery, multiple dilatations, and uterine anomalies can also contribute to an increased risk of PTB.[6] Regarding maternal demographic characteristics, age (<17 or >35 years), low education level, low socioeconomic status, single marital status, short inter-pregnancy interval, and genetics are related to an increased risk of PTB.[6,8] Furthermore, in addition to multiple gestations and short cervix, current pregnancy-related risk factors include prior surgery on the cervix (e.g., termination of pregnancy, spontaneous abortion), assisted reproductive techniques, vaginal bleeding, polyhydramnios or oligohydramnios, maternal comorbidities (e.g., hypertension, preeclampsia, diabetes, thyroid disease), mental health issues (e.g., stress, depression, anxiety), maternal nutrition status, infections (e.g., bacterial vaginosis, trichomoniasis, chlamydia, gonorrhea), inflammation, positive fetal fibronectin, and uterine contractions.[6,10] Lastly, some adverse behaviors, like tobacco use, excessive alcohol consumption, and drug abuse, also increase the risk of PTB (See Table 1.2).[6,8,10]

Table 1. 2 Risk Factors for PTB

Classification	Risk Factors
Maternal demographics	Age (<17, or >35 years)
	Race (Black)
	Low BMI
	Low education level
	Low socioeconomic status
	Single marital status
	Short inter-pregnancy interval
Prior obstetric history	Genetics
	Prior PTB
	Cervical surgery
Current pregnancy characteristics	Short cervix
	Multiple gestations
	Assisted reproductive techniques
	Vaginal bleeding
	Volyhydramnios or oligohydramnios
	Maternal comorbidities (e.g. diabetes, hypertension)
	Mental health issues (e.g. stress, depression)
	Poor nutrition status
	Infections
	Inflammation
	Positive fetal fibronectin
	Uterine contractions
Adverse behaviors	Tobacco use
	Excessive alcohol consumption
	Drug abuse

Source: Adapted from Berghella V. Preterm birth: prevention and management. Chapter 4. P28. John Wiley & Sons; 2010.[6]

1.6 Prevention of PTB

Overall, there are three types of prevention—primary, secondary, and tertiary preventions. Primary prevention mainly involves preventing exposure to hazards, which may target prepubertal girls to educate them and optimize their health, women who plan to get pregnant to raise their awareness and maintain healthy lifestyles, and even men who are a sexual partner of targeted women. This education may involve: raising awareness of

significance of PTB; exercising and a healthy diet to arrive at an ideal BMI; ensuring adequate nutrition and using dietary supplementation (folate acid, vitamins, calcium, zinc, etc.) if needed; decreasing unplanned pregnancies; avoiding tobacco, alcohol, and illicit drug use; minimizing stress; preventing sexually transmitted infections; and limiting the number of embryos transferred during in vitro fertilization (IVF).[6]

Different from primary prevention, secondary and tertiary prevention are easier to track, and effectiveness is more readily identified. Hence, healthcare providers and pharmaceutical companies put more emphasis on secondary and tertiary prevention strategies. The purpose of secondary prevention is to detect a disease early and prevent it. Receiving screening or predictive tests, such as physical examinations or ultrasonography examinations, fetal fibronectin (fFN) tests, or placental alpha macroglobulin-1 (PAMG-1) tests may be helpful in detecting abnormalities for an asymptomatic population.[6]

Tertiary prevention focuses on women with signs or symptoms of preterm delivery. Several major tertiary prevention strategies of SPTB include the use of progesterone, cervical cerclage, tocolytics, and antibiotics. The choice of these different approaches is based on various risk factors that are identified. Progesterone supplementation has been shown to be effective for women with a history of SPTB or with a short cervix. Cervical cerclage is suggested to be implemented among women with a short cervix, which refers to putting a suture into or around the cervix in order to treat cervical insufficiency.[62,63] Cerclage has also been shown to be effective for women with a history of SPTB.[63] Tocolytic medications are used to suppress contractions when early labor begins and typically delay birth for 2 to 7 days.[64] When a fetus is in immediate danger, tocolytics ought not to be administered. Tocolytics may also

serve as adjunctive therapy to progesterone and cervical cerclage.[10] For women with symptoms of infections, corresponding antibiotics are suggested for PTB prevention. Antibiotic therapy has been shown to prolong the interval of time from membrane rupture to delivery for patients with PPROM.[65]

In summary, PTB results in tremendous clinical and economic burden, and, thus, it is significant to investigate how to effectively prevent PTB. Among three types of prevention, tertiary prevention strategies have been involved in most research, because women usually go to see physicians when the symptoms of PTB appear, and the effectiveness of tertiary prevention is easier to measure. Simultaneously, tertiary prevention strategies are the most expensive, compared to primary and secondary prevention strategies, so it is important to evaluate their effectiveness. Since SPTB is the most common type of PTB (accounting for 2/3 of PTBs), and progesterone supplements, as one of the main tertiary prevention strategies, was recommended for all women with history of PTB to prevent SPTB,[66] more information about progesterone and 17-α-hydroxyprogesterone caproate (17-OHPC) is discussed in the next chapter.

Chapter 2 Literature Review

2.1 Progesterone and 17α-Hydroxyprogesterone Caproate (17-OHPC)

2.1.1 Introduction of Progesterone and 17-OHPC

Progesterone, one of the progestogens in humans, is a natural sex steroid produced by the corpus luteum during the first trimester of pregnancy. It plays a crucial role in the maintenance of early pregnancy through 7 to 9 weeks of gestation. Subsequently, the corpus luteum begins to decrease in size and the placenta takes over progesterone production to support gestation and inhibit uterine activity.[67-69] Progestin is usually mixed with progesterone, which is a synthetic analog of natural progesterone structure. Thus, strictly, 17α-hydroxyprogesterone caproate (17-OHPC) is a synthetic compound, which is progestin rather than progesterone. However, some researchers categorize progesterone as synthesized and natural progesterone (or natural micronized progesterone).[69,70] From this perspective, 17-OHPC can be seen as a subtype of progesterone.

A common abbreviation of 17α-hydroxyprogesterone caproate is 17-OHPC or 17P. However, it is inaccurate to use 17P as the abbreviation for 17-α hydroxyprogesterone caproate, since 17P is also the abbreviation of 17α-hydroxyprogesterone, which is a natural steroid produced by the ovaries, and does not contain the caproate molecule.[68]

2.1.2 Mechanism of Progesterone and 17-OHPC

The molecules for natural progesterone and 17-OHPC are different, as are their mechanisms of action. Progesterone receptor A (PR-A) and Progesterone receptor B (PR-B) are two predominant forms of receptors that play important roles during pregnancy. Binding PR-B and progesterone will stimulate the transcription of genes that promote uterine relaxation;

and PR-A is a repressor of PR-B function, which is related to the onset of labor.[71] Through mediation of PR-A and PR-B, progesterone exerts its action in "relaxation of myometrial smooth muscle, blocking of the action of oxytocin and inhibition of the formation of gap junctions between myometrial cells."[72] In another words, progesterone is helpful in reducing the contraction of myometrial muscles so as to maintain pregnancy. Progesterone also exerts an impact on anti-inflammation through the inhibition of monocyte chemoattractant protein-1 (MCP-1).

In contrast, the mechanism of 17-OHPC is not fully understood. Although one study found that 17-OHPC had some anti-inflammatory effects,[73] compared to vaginal progesterone, 17-OHPC does not appear to have a significant anti-inflammatory effect.[74] Moreover, unlike progesterone, 17-OHPC does not have an effect on the myometrium or uterine contractions.[65,71] Nonetheless, the primary effect of 17-OHPC in preventing PTB seems to be on the cervix. Studies found 17-OHPC can delay cervical collagen degradation, and it is associated with less cervical shortening clinically.[65] Still, the specific mechanism of 17-OHPC needs further exploration.

2.1.3 Dosage Forms of Progesterone and 17-OHPC

Progesterone supplements are available in the form of vaginal gel, vaginal suppository, oral capsule, and intramuscular injection. Natural progesterone can be supplied in any of the first three forms, while synthesized progesterone is only supplied as an intramuscular injection.[70] The dosage, use interval, and duration of effects also differ for the various dosage forms of progesterone supplement therapy (See Table 2.1).

Table 2. 1 Route, Dose, Interval and Duration of Different Progesterone Supplement Therapy

Drug Type	Route	Dose	Interval	Duration	References
17-OHPC	Intramuscular injection	250mg	Weekly	Start 16-20 weeks, until 36 weeks or delivery	75,76
Natural micronized progesterone	Vaginal gel	45mg (4% gel), 90mg (8% gel)	Daily	Start 18-24 weeks of gestation, until 36-37 weeks of gestation	52,77,78
	Vaginal suppository	100mg, 200mg, 400mg	Daily	Start 16-24 weeks of gestation, until 34-36 weeks of gestation	79-83
	Oral capsule	200mg, 400mg	Daily	Start 18-24 weeks of gestation, until 33-36 weeks of gestation	84,85

Source: Adapted from Choi SJ. Use of progesterone supplement therapy for prevention of preterm birth: review of literatures. *Obstetrics & Gynecology Science*. 2017;60(5):405-420. 70

2.1.4 Branded vs. Compounded 17-OHPC

Before the 1990s, 17-OHPC was marketed under the brand names Delalutin™ and Hydrogest™. However, due to controversy of the effectiveness in preventing PTB, these products were discontinued. After approximately 20 years of development, the U.S. Food and Drug Administration (FDA) approved the use of 17-OHPC in preventing recurrent SPTB under the brand name Makena™ in 2011.65 In addition to Makena™, compounded 17-OHPC is available in U.S. pharmacies. There are only a few studies investigating the effectiveness of compounded 17-OHPC, with results showing administration of the compounded version of 17-OHPC to be safe and effective,86 and no significant difference in the PTB rate was found between the branded and compounded drug.87 Even though the use of compounded 17-OHPC is not recommended by the FDA, there is no enforcement against pharmacies that provide

compounded alternatives due to patient access concerns and special medical needs.[65,71] Moreover, under section 503A of the Federal Food, Drug, and Cosmetic Act, "a pharmacist may not compound regularly or in inordinate amounts any drug products that are essentially copies of Makena."[88]

2.2 Clinical Evidence on Efficacy of 17-OHPC in Preventing SPTB

Since the 1950s, progestin supplementation has been studied as a means to prevent PTB.[65] Goldstein et al. (1989) conducted a meta-analysis to evaluate the efficacy of progesterone and other progestogenic agents. This meta-analysis included 15 randomized control trials (RCTs) published between 1975 and 1980, with the conclusion that progestogens having no impact on any pregnancy outcomes, which was measured by rate of PTB and rate of miscarriage.[89] However, since different forms of progestogenic agents may have different effectiveness in the prevention of SPTB, Keirse et al. (1990) conducted a meta-analysis assessing effectiveness of 17-OHPC with stricter inclusion criteria (e.g., using data from placebo-controlled trials). They concluded there was no support for the role of 17-OHPC in the prevention of miscarriage, but it may be effective for PTB prevention (OR=0.50, 95% CI=0.30-0.85).[90]

A noteworthy large multicenter double-blind placebo-controlled trial was conducted by Meis et al. (2003) with the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network (NICHD) to examine the efficacy of 17-OHPC in preventing recurrent SPTB. The study included 463 women, with 310 (67.0%) receiving weekly injections of 250mg of 17-OHPC and 153 (33.0%) receiving a placebo until delivery or 36 weeks of gestation. Results showed the incidence of delivery before 37 weeks of gestation

was 36.3% in the treatment group versus 54.9% in the placebo group (RR=0.66, 95% CI=0.54-0.81), which indicated that injections of 17-OHPC may significantly reduce the risk of recurrent SPTB.[75] This conclusion was similar to one provided by Saghafi et al. in 2011. By analyzing 100 women with a history of PTB, they found weekly administration of 17-OHPC was significantly associated with a decrease in preterm delivery (p=0.011) and improvement in neonate birth weight (p=0.02).[76]

However, the efficacy of 17-OHPC is still a controversial topic for pregnant women with different risk characteristics. Combs et al. (2015) tested the effectiveness of 17-OHPC in women with preterm premature rupture of membranes (PPROM). The primary outcome was birth at a favorable gestational age (32 to 34 weeks), but only 3% of the treatment group achieved this outcome, and there was no significant difference between the treatment and control groups (p=0.18).[91] Winer et al. (2015) found that among women with a cervical length less than 25mm and a history of PTB, cervical surgery, or uterine malformation, 17-OHPC showed no impact in prolonging pregnancy. When varying the cut-off definition to 32, 34, or 37 weeks, again no significant differences were found.[92] The efficacy of 17-OHPC may also vary according to the weight of women. Heyborne et al. (2015) performed a secondary analysis from Meis's trial[75] to examine if body mass index (BMI) modified the effectiveness of 17-OHPC. Results showed 17-OHPC is only effective for women with pre-pregnancy BMI < 30 kg/m2 (RR=0.54, 95% CI=0.43-0.68). When the researchers used only maternal weight instead of BMI, 165lb was the observed threshold above which 17-OHPC was not effective.[93]

None of above studies included women with multiple gestation, which is known to increase the risk of PTB. However, there are studies focusing on exploring the efficacy of 17-

OHPC for women with multiple gestation. Awwad et al. (2015) selected 288 women with twin pregnancies to carry out a RCT. Results indicated injection of 17-OHPC did not reduce PTB in twin pregnancies. Nevertheless, as the secondary outcome, neonatal morbidity was found to be significantly lower in the 17-OHPC group (19.1%) than the placebo group (30.9%) (OR = 0.53, 95% CI = 0.31-0.90), and the birthweights of neonates were increased.[94] Furthermore, two studies reported that among women with triplet pregnancies, gestational age at delivery and neonatal morbidity was not influenced by 17-OHPC.[95,96]

The concentration of 17-OHPC may also influence its effectiveness. Caritis et al. (2014) used blood samples obtained from 315 women with a SPTB. Their plasma concentrations of 17-OHPC ranged from 3.7 to 56ng/ml, and low plasma 17-OHPC concentrations were associated with an increased risk of SPTB. Women with the lowest quartile plasma concentrations had a significantly higher risk of SPTB (p=0.03).[97] However, a prospective cohort study reached different conclusions—no significant difference was found in median 17-OHPC levels between women who delivered before 35 weeks and after 35 weeks of gestation.[98] A weekly injection of 250mg 17-OHPC is the regulated dosage as specified by Makena's manufacturer,[99] and this dosage was used in previous studies. However, no data suggest a dose adjustment based on patient BMI or any other patient-specific indexes, nor are there published guidelines that specify the optimal dose of 17-OHPC. Genotype may also play a role in the efficacy of 17-OHPC. Manuck et al. (2017) claimed that human progesterone receptor gene polymorphisms can alter the clinical efficacy of 17-OHPC in the prevention of PTB.[100]

It is also noteworthy that a confirmatory phase 3B RCT of 17-OHPC versus vehicle for prevention of PTB ["Progestin's Role in Optimizing Neonatal Gestation (PROLONG),"

NCT01004029] completed in 2018, which was initiated in 2009 and funded by AMAG (the manufacture of "Makena™"), and it did not demonstrate a statistically difference in the incidence of PTB between the treatment and placebo group (p=0.72).[101,102] To date, no manuscript has been published based on this clinical trial. Since more than 75% of patients were enrolled outside the U.S., and mainly from Eastern European countries, Julie Krop, AMAG's Chief Medical Officer said, "In light of the recent findings and the inconsistencies with prior clinical evidence, we plan to conduct additional subgroup analyses of the PROLONG data, particularly focusing on patients at the highest risk of preterm delivery and the subset of patients enrolled in the U.S."[102]

2.3 Clinical Evidence on Efficacy of Vaginal Progesterone in Preventing SPTB

The efficacy of vaginal progesterone in reducing PTB rates and improving neonatal outcomes among high-risk pregnant women, either with a history of PTB or with a short cervix, has been assessed by numerous RCTs which compared vaginal progesterone to placebo. The PTB rates in patients with vaginal progesterone (no matter in the form of gel, suppository, or capsule) ranged from 2.7% to 19.2% and differed significantly with placebo groups, with PTB rates ranging from 18.5% to 34.3%.[79,81] O'Brien et al. (2007) found that vaginal progesterone showed no effect on women with a history of PTB,[77] but they used a PTB cut-off of 32 weeks, where other studies selected 34 or 35 weeks, which may explain the difference in results.

In addition to comparisons with placebo, the efficacy of vaginal progesterone was also compared to 17-OHPC injections in reducing SPTB rate by a number of studies. Maher et al. (2013) compared vaginal gel to 17-OHPC among women with a history of PTB and without a short cervix on the SPTB rate at 34 weeks, 32 weeks, and 28 weeks. For all three cut-off points,

vaginal progesterone gel was significantly more effective in reducing the rate of PTB. The PTB rates(< 34 weeks) for the vaginal gel group and the 17-OHPC group were 16.6% vs. 25.7% (p= 0.02).[78] However, in Bafghi et al.'s study in 2015 (which included women either with a history of PTB or a short cervix),[80] Norman et al.'s study in 2016 (which included women either with a history of PTB or a short cervix),[83] Pirjani et al.'s study in 2017 (which included women with a short cervix only)[81] and Elimian et al.'s study in 2016 (which included women with a history of PTB only),[103] no significant differences between vaginal progesterone and 17-OHPC were identified for the rate of SPTB or neonatal outcomes.

Based on various results from RCTs, researchers also conducted systematic reviews and meta-analyses comparing vaginal progesterone and 17-OHPC outcomes. A meta-analysis was conducted by Saccone et al. (2017) to compare vaginal progesterone with 17-OHPC for prevention of recurrent SPTB in singleton gestations. No significant differences were identified in the rate of SPTB < 37 weeks, < 28 weeks, and < 24 weeks. However, women in the vaginal progesterone group had a significantly lower rate of SPTB < 34 weeks and < 32 weeks. In addition, a lower rate of neonatal intensive care unit admission was observed in the vaginal progesterone group. Nevertheless, only three studies were included in the analysis, and the authors also pointed out the quality level of the studies was low, so the results may not be robust.[104] Romero et al. (2014) also published a review on the comparison of the two drugs. They concluded that vaginal progesterone is effective in women with a short cervix both with and without a prior history of PTB; while 17-OHPC is only effective for women with a prior PTB, but not for women with a short cervix.[105]

2.4 Guideline on the Use of 17-OHPC in Prevention of SPTB

Based on the results from clinical trials on efficacy of 17-OHPC and vaginal progesterone, several guidelines on use of 17-OHPC and/or vaginal progesterone have been published. In 2012, The American College of Obstetricians and Gynecologists (ACOG) published a guideline on prediction and prevention of PTB. As for the clinical recommendation for management of women with a singleton pregnancy and a prior spontaneous preterm delivery, the guideline suggests "offering progesterone supplementation starting at 16-24 weeks of gestation to reduce the risk of recurrent spontaneous preterm birth." In this context, the progesterone supplementation referred to 17-OHPC (250mg weekly injections), vaginal progesterone suppository (100mg daily), vaginal progesterone gel (90mg daily), and micronized vaginal progesterone capsules (200mg daily). However, for asymptomatic women with a short cervix who do not have a history of PTB, only cerclage and vaginal progesterone were recommended. On the other hand, for women with a singleton pregnancy who did not have a prior PTB and have normal or unknown cervical length, progesterone treatment is not recommended. For women with multiple gestations, currently, no available approach is found to be effective in reducing their risk of PTB.[106]

The Society for Maternal-Fetal Medicine (SMFM) committee also published a guideline in 2017 on the prevention of SPTB in women with a singleton pregnancy. For this particular group of women, weekly injections of 250mg 17-OHPC were recommended, starting at 16-20 weeks until 36 weeks of gestation or delivery. However, inconsistent with ACOG's guideline, vaginal progesterone was not recommended as a substitute for 17-OHPC.[66]

Another guideline published in 2011 for the management of SPTB is endorsed by the

European Association of Perinatal Medicine (EAPM). Similar to ACOG's guideline, microionized progesterone and 17-OHPC are recommended for asymptomatic women presenting with a prior history of PTB. However, the initiation time of injection is not specified in this guideline. In multiple pregnancies, neither microionized progesterone nor 17-OHPC was recommended. In spite of this, it is worth noting that in contrast to the ACOG's guideline, in single pregnant nulliparous women with a short cervix, both microionized progesterone and 17-OHPC are recommended. The guideline also indicated that only two quality studies performed in few subjects support this intervention; hence, more research is required.[107]

2.5 Utilization of 17-OHPC among Eligible Women from Different States

The coverage policies and utilization of 17-OHPC vary across different states. Batra et al. (2017) conducted a cross-sectional study and offered a web-based survey to identify variations in progesterone coverage guidelines in different state Medicaid managed care organizations (MMCOs). Eighteen managed care organizations (MCO) plans provided coverage for 31 of the 39 states with MMCOs. Out of 18 MCO plans, 87.5% of respondents covered branded progesterone and 81.3% covered compounded progesterone. MMCO coverage policies varied across states: 86.7% of plans required prior authorization (PA) for branded 17-OHPC and 75% required PA for compounded 17-OHPC.[108]

The Association of State and Territorial Health Officials (2015) published an issue brief on the state and territorial health agencies' practice of promoting 17-OHPC access and use. Therein, Louisiana, North Carolina, Ohio, Texas, Iowa, and South California are actively playing a role in collaborating with Medicaid agencies, enhancing the ordering and administration process, improving education and partnering with key stakeholders.[109]

Louisiana Medicaid began reimbursing the administration of 17-OHPC in 2010. But data from the Louisiana Department of Health and Hospitals indicated that only 4.67% of women at risk for recurrent PTB received 17-OHPC in 2011, and this number increased slightly to 7.41% in 2013.[110]

North Carolina has had a strong statewide 17-OHPC initiative since 2007. Injection of 17-OHPC is covered by North Carolina Medicaid, but the prerequisite is women have to receive injections at the clinic. Stringer et al. (2016) conducted a retrospective cohort study investigating the utilization of 17-OHPC among eligible women delivering at two major North Carolina hospitals. Results showed only 47% of eligible women received ≥ 1 injection. For those who were covered, the median number of injections was 9.[111]

Cross-Barnet et al. (2018) used data from Center for Medicare and Medicaid Innovation, which launched Strong Start programs from 2013 to 2017, and 27 awardees from over 200 sites in 30 states participated. They reported that 14.95% of 45,999 eligible enrolled patients received 17-OHPC.[135]

2.6 Medication Adherence of 17-OHPC

The medication adherence of 17-OHPC and factors related to adherence have not been well investigated in the real-world setting. Furthermore, since low medication adherence may reduce the effect of 17-OHPC in the prevention of SPTB, it is also necessary to explore the association between patients' adherence and effectiveness of 17-OHPC. According to the guidelines, weekly injections of 17-OHPC should start between 16 and 24 weeks of gestation and continue until 36 weeks or delivery. Thus, when evaluating adherence, at least 10-12 injections during the pregnancy process are needed to ensure women receiving 17-OHPC in

the recommended gestational window.

Different definitions of 17-OHPC adherence were applied across different studies. Rittenberg et al. (2007) identified patients who did not continue 17-OHPC injections as non-adherers. They conducted a retrospective review assessing adherence to 17-OHPC in the community setting. Among the included patients, 59 out of 1,979 (3%) discontinued injections after a single injection, and 474 out of 1,979 (24%) discontinued before 34 weeks of gestation.[112] The authors were not able to specify reasons for patients' discontinuation. Yee et al. (2016) defined adherence as no more than one missed dose to evaluate the association between adherence to 17-OHPC and ethnic disparities at a single institution. Of 472 women, 83% of women were adherent to 17-OHPC. For women who were nonadherent, they were more likely to be non-Hispanic Black and have public insurance.[113] Carter et al. (2019) measured the adherence by calculating the number of injections received divided by the number of eligible injections patients may receive from the initiation date to the delivery date. MarketScan data was used to explore the association between timing of 17-OHPC initiation and PTB risk. Instead of defining a cut-off of adherence, they reported the number and percentage of patients in each adherence rate range. The results showed that of 3,374 patients, 32.3% had an adherence rate over 85% and 54.3% had an adherence rate over 60%.[114] DeNoble et al. (2019) used the similar way to measure adherence, and they chose 70% as the minimum threshold for adherence, with the reason that this would the proportion if patients receive injections with at the maximum interval of 10 days between doses. They reported a 72.2% adherence rate with a sample size of 115 patients from a Duke University-affiliated hospital.[115]

Three studies using Medicaid data were identified. Lucas et al. (2012) evaluated the

adherence with guidelines by reporting the proportion of patients initiating 17-OHPC within the recommended window of gestational age (16-20.9 weeks of gestation). Using data collected from one of Centene's managed Medicaid programs, they found that 58.6% of 790 patients initiated 17-OHPC in the recommended gestational age window, and 9.2% initiated 17-OHPC after 26 weeks of gestation.[116] Orsulak et al. (2015) defined adherence as receiving at least 10 injections. Using Louisiana Medicaid data, they reported that 301 out of 4,091 (7.4%) eligible women received at least one injection of 17-OHPC in 2013, and only about half of this small cohort received more than 10 doses. The mean number of doses per patient was 8.3.[110] Hydery et al. (2017) defined proportion of days covered (PDC) of 0.8 or more as the cut-off for adherence to investigate the outcomes and adherence of 17-OHPC in Massachusetts Medicaid. They found that 66.3% of the population was adherent; and medication adherence was not significantly associated with the rate of PTB. The study included a limitation of the possible overestimation of adherence.[117]

In terms of factors that may be associated with adherence, maternal age was reported to be associated with adherence in several studies. In Haidar et al.'s study (2017), only age was found to be associated with adherence, with women in the 100% compliance group older than those in the 40-80% compliance group.[118] Sutton et al. (2018) and DeNoble et al. (2019) also found that women with older maternal age were more likely to be adherent to 17-OHPC.[115,119] Additionally, Berhie et al. stated that non-Hispanic Black women received fewer 17-OHPC doses than White women, without statistically significant differences.[120] Non-Hispanic Black women were reported to have more missed doses ($p<0.001$) and had later initiation of care ($p<0.001$), as detailed by Yee et al.[113] Carter et al. (2019) found that a higher number of prior

PTBs was related to early 17-OHPC initiation; but other factors, including maternal age and different types of comorbidities, were not shown to be related to the timing of 17-OHPC initiation.[114] In Hydery et al.'s study, race, number of comorbidities, and different types of comorbidities were not shown to be associated with adherence.[117]

In summary, the adherence to 17-OHPC reported in the literature ranges between 33% and 83%. The reported adherence is higher from studies with a small sample size of population from one medical center/institution, compared to studies with a larger, more diverse sample. Table 2.2 summarizes studies on evaluation of 17-OHPC adherence.

Table 2. 2 Summary of Studies on Evaluation of 17-OHPC Adherence

Author	Year	Study Design	Sample Size	Adherence Definition	Results
Rittenberg et al.[112]	2007	Retrospective view; in the community setting	1979	Not adherent: not continue 17-OHPC injections	24% discontinued before 34 weeks of gestation (76% adherent)
Lucas et al.[116]	2012	Retrospective cohort study; Centene's managed Medicaid programs	790	Adherent: initiated 17-OHPC in the recommended gestational age window (16-24 weeks of gestation)	58.6% adherent
Orsulak et al.[110]	2015	Retrospective cohort study; Louisiana Medicaid	301	Adherent: >=10 doses injections	51.4% adherent
Yee et al.[113]	2016	Retrospective cohort study; at a single institution	472	Adherent: no more than one missed dose	83% adherent
Hydery et al.[117]	2017	Retrospective cohort study; Massachusetts Medicaid	169	Adherent: proportion of days covered (PDC) >=0.8	66.3% adherent
DeNoble et al.[115]	2019	Retrospective cohort study; EMR data from a Duke University-affiliated hospital	115	Adherence rate=number of received injections/number of eligible injections; adherent: 70%	72.2% adherent
Carter et al.[114]	2019	Retrospective cohort study; MarketScan database	3374	Adherence rate= number of received injections/number of eligible injections; adherent: no cut-off	32.3% had an adherence rate over 85%; 54.3% had an adherence rate over 60%.

2.7 Outcome Research on Effectiveness of 17-OHPC in Preventing SPTB

Although 17-OHPC was shown to be effective in several clinical trials and is recommended by guidelines for the prevention of recurrent SPTB, different demographic characteristics and medication adherence may affect the effectiveness of 17-OHPC. Therefore, outcomes research is necessary to assess the effectiveness of 17-OHPC in real-world settings.

As for measuring the outcomes, the rate of PTB is usually used as the primary outcome, and duration of pregnancy and neonatal morbidity are often secondary outcomes. Most studies used 37 weeks of gestation as the cut-off point for PTB. Some studies have conducted sensitivity analyses at 35 weeks, 34 weeks, 32 weeks, and/or 28 weeks. Petrini et al. (2005) used 2002 national birth certificate data from New Jersey and Missouri to estimate the number of eligible women, rate of recurrent SPTBs, and potential reduction in the national PTB rate. They used a 33% reduction in PTB (reported by Meis et al.'s study[75]) to estimate the effect. The result showed the overall U.S. PTB rate would decrease by approximately 2% ($p<0.001$) with use of 17-OHPC, a modest effect on the national PTB rate.[121] Rittenberg et al. (2007) conducted a retrospective review on data collected from an outpatient 17-OHPC administration program provided by Matria Healthcare from 2004 to 2006. For women who received 17-OHPC, 37.3% experienced SPTB, 22.1% delivered at less than 35 weeks, and 9.0% delivered at less than 32 weeks.[112] Hydery et al. (2017) conducted a retrospective cohort study using Massachusetts Medicaid data from 2011 to 2015, and the primary outcome was term delivery at 37 weeks. They found that 62.1% of patients receiving progesterone had a term delivery, which is consistent with progesterone effectiveness obtained from clinical trials.[117]

However, the three studies above only described the percentage of patients having PTB

among patients receiving 17-OHPC, instead of testing the difference in PTB rate between patients with and without 17-OHPC. Turitz et al. (2016) performed a cross-sectional study from 2009 to 2013, and no difference in rate of SPTB was observed between women who did and did not use 17-OHPC (37.2% vs. 34.0%, p=0.7). Moreover, the utilization of 17-OHPC was not associated with patients' race, obesity, or insurance status.[122] Nelson et al. (2017) conducted a prospective cohort study from 2012 to 2016 in a single medical center. By using recurrence of birth ≤ 35 weeks as the primary outcome, the overall rate of recurrent PTB was 25.0% compared to the expected rate 16.8% (p=1.0).[98] DeNoble et al. (2019) compared the PTB rate by receipt of 17-OHPC, and no significant difference in PTB rate was observed between patients with or without 17-OHPC (25.7% vs. 28.6%, p=0.52).[115]

Using duration of pregnancy as the outcome, Bastek et al. (2012) conducted a cross-sectional study of PTB rate and gestational age distribution at delivery from 2004 to 2009 at an urban academic medical center at Pennsylvania. Results showed administration of 17-OHPC resulted in a 10-day shift of gestational ages (31.6 to 33.1 weeks) toward delivery at late preterm (OR = 2.3, 95% CI = 1.49–3.54).[123] A secondary analysis of women enrolled in Meis et al.'s study[75] was conducted by Spong et al. (2005). This study also concluded that 17-OHPC can prolong pregnancy overall (38.0 weeks vs. 36.7 weeks, p=0.004), especially for women with a prior SPTB before 34 weeks of gestation.[124] However, Nelson et al. (2017) found no significant difference in weeks of gestation (p=0.63).[98] Table 2.3 summarized studies on effectiveness of 17-OHPC in the real-world settings.

Table 2. 3 Summary of Real-World Evidence on Effectiveness of 17-OHPC

Author	Year	Data Source	Research Type	Delivery Outcome	Results
Petrini et al.[121]	2005	National birth certificate data from New Jersey and Missouri	Retrospective study	PTB rate	For the overall U.S., use of 17-OHPC has a modest effect on the national preterm birth rate (2% decrease).
Rittenberg et al.[112]	2007	Matria Healthcare	Retrospective cohort study	PTB rate	For women who received 17-OHPC, 37.3% experienced SPTB; 22.1% delivered at less than 35 weeks; and 9.0% delivered at less than 32 weeks.
Bastek et al.[123]	2012	An academic medical center at Pennsylvania	Cross-sectional study	Duration of pregnancy	Administration of 17-OHPC caused a 10-days shift of gestational ages toward delivery at late preterm (OR = 2.3, 95% CI = 1.49–3.54).
Turitz et al.[122]	2015	A specialty prematurity clinic	Cross-sectional study	PTB rate	No difference in rate of PTB was observed between women who used and did not use 17-OHPC (37.2% vs. 34.0%, p=0.7).
Hydery et al.[117]	2017	Massachusetts Medicaid	Retrospective cohort study	PTB rate	62.1% of patients receiving progesterone had a term delivery.
Nelson et al.[98]	2017	Parkland hospital	Prospective cohort study	PTB rate; duration of pregnancy	17-OHPC was ineffective for prevention of recurrent PTB in terms of both PTB rate (p=1.0) and duration of gestation (p=0.63).
DeNoble et al.[115]	2019	Duke University affiliated hospital	Retrospective cohort study	PTB rate	No significant difference in PTB rate was observed between patients with or without 17-OHPC (25.7% vs. 28.6%, p=0.52).

The association between medication adherence and the outcome of 17-OHPC has been also investigated. Low adherence rates are thought to reduce the effectiveness of 17-OHPC in several studies. Rebarber et al. (2007) conducted a retrospective cohort study to identify the effect of early cessation of 17-OHPC. They identified eligible women who initiated 17-OHPC at 16-20 weeks gestational age. One group terminated the use of 17-OHPC before 32 weeks, and the other group received injections until delivery or 37 weeks. They concluded that early cessation of 17-OHPC injection was associated with an increased risk of recurrent SPTB, using endpoints of 37 weeks (48.1% vs. 33.3%, p=0.01), 35 weeks, or 32 weeks of gestation.[125] Ning et al.'s study (2017) suggested women with early-start 17-OHPC (14-16 weeks) have lower rates of recurrent PTB <37 weeks, compared to those with late-start 17-OHPC (17-27 weeks) (41.3% vs. 57.7%, P = 0.065). Women with early 17-OHPC initiation also had lower rates of major neonatal morbidity (1.5% vs. 14.3%, p=0.005).[126] Carter et al. (2019) reported that less adherent patients (receiving <25% of recommended doses) were more likely to have PTB than those receiving >85% of recommended doses (aRR=0.15, 95%CI=1.2-1.7, p=0.01).[114] However, some studies reported no association between adherence and outcome of 17-OHPC. Lucas et al. (2012) found no significant difference in SPTB rate for women initiating 17-OHPC at an early gestational age (16-20.9 weeks) versus those initiating after 20.9 weeks (34.3% vs. 36.1%, p=0.61).[116] Haidar et al. (2017) conducted a secondary analysis based on a prospective study which categorized women into two groups—one with a 100% compliance rate (full compliance, n=370) and another with a 40%-80% compliance rate (partial compliance, n=35). By comparing the two groups, they concluded that injections of 17-OHPC significantly decreased recurrent PTB in both groups, but no significant differences in neonatal outcomes

were found (27.0% vs. 31.3%, p=0.52).[118]

In summary, currently, no consensus has been reached on the effectiveness of 17-OHPC in terms of either reducing recurrent SPTB rate, prolonging women's duration of pregnancy, or improving neonatal birth outcomes. Hence, it is still necessary to conduct more research using large databases to investigate the real-world effectiveness of 17-OHPC.

2.8 Adverse Effects of 17-OHPC

In addition to effectiveness of 17-OHPC, both clinical trials and outcomes studies reported adverse effects of 17-OHPC. Since adverse effects may also be one of the reasons for underutilization and inadequate medication adherence of 17-OHPC, it is necessary to study the relationship between use of 17-OHPC and incidence of adverse effects. Most side effects of 17-OHPC are injection-site related reactions. In Meis et al.'s trial (2003), 50% of patients reported at least one adverse side effect, including injection site soreness (34.2%), swelling (14.1%), itching (11.3%), and bruising (6.7%). Women in the 17-OHPC group were significantly more likely to have swelling and a lump at the injection site compared to the placebo group.[75] In an RCT using 17-OHPC (2009), 35% of participants reported injection site pain, 17% experienced injection site swelling, 12% had urticaria; and the incidences of pruritus, nausea and vomiting, and injection site nodule were 8%, 6%, and 4%, respectively.[127]

In addition to injection-site related reactions, some maternal complications may be also associated with use of 17-OHPC. One potential risk of 17-OHPC is that it may be related to a higher risk of gestational diabetes mellitus (GDM). Theoretically, progestogens can alter the physiology of glucose transport into cells and may also impact the release of insulin.[128] Rebarber et al. (2007) found that for patients with similar maternal BMI and age, the incidence

of GDM was higher for women receiving 17-OHPC (OR=2.9, 95% CI=2.1-4.1).[125] This seems also applicable to obese women. Egerman et al. (2014) retrospectively identified obese singleton pregnant women with BMI ≥ 30 kg/m2, excluding women with history of diabetes or GDM during previous pregnancies. The analysis results showed that for obese women greater than 35 years old, early initiation of 17-OHPC may increase the risk of GDM (13.8% vs. 9.6%, p=0.048).[129] A prospective cohort study conducted by Nelson et al. (2017) also reported that the use of 17-OHPC was associated with an increase of gestational diabetes (13.4% vs. 8%, p=0.001).[98] The association between GDM and the use of 17-OHPC has been disputed, however, Gyamfi et al. (2009) conducted a secondary analysis of a clinical trial, which included 1094 women with 411 singleton and 653 twin pregnancies. Either in singleton or twin pregnancies, no association was found between higher rates of GDM and administration of 17-OHPC.[128] A similar conclusion was also made by Rouholamin et al (2015).[130]

Gestational hypertension (GHT) and preeclampsia are also listed on the Makena billing guide listed as possible maternal complications of Makena based on the results from Meis's clinical trial (8.8% in the treatment group versus 4.6% in the control group).[75,99] However, the effect of 17-OHPC in decreasing blood pressure has been noted in recent literature. Sammour et al. (2005) indicated that the prevention of hypertensive disorders seemed possible by using progesterone.[131] Ngai et al. (2014) evaluated the association between preeclampsia and 17-OHPC, with concerns that 17-OHPC may increase the risk of preeclampsia. However, no association was found between incidence of preeclampsia and 17-OHPC, with preeclampsia incidence of 2.5% in the treatment group and 5.6% in the control group (p=0.27).[132] The study conducted by Amaral et al. (2015) illustrated that 17-OHPC's effect of decreasing blood

pressure made it possible to be considered as a viable addition to preeclampsia treatment.[133] Cottrell et al. (2019) found that 17-OHPC could improve hypertension in response to elevated soluble fms-like tyrosine kinase-1.[134]

Thus, more studies need to be conducted to confirm the relationships between incidence of GDM, GHT, or preeclampsia and 17-OHPC utilization.

2.9 Summary of Literature Review

In summary, 1) 17-OHPC is recommended by guidelines to prevent recurrent SPTB; however, overall, it is underutilized; 2) there is no consensus on the effectiveness of 17-OHPC for preventing SPTB in real-world settings; 3) few studies have investigated adherence rates of 17-OHPC and no consistent definition was applied to evaluate 17-OHPC adherence across different studies; 4) the consequences of low medication adherence have not been adequately addressed; 5) there is no consensus regarding the association of the incidence of GDM, GHT, or preeclampsia and the use of 17-OHPC.

2.10 Study Aim

This study aims to address gaps in the literature by: 1) evaluating the utilization of 17-OHPC among eligible women using Decision Resources Group (DRG) databases; 2) comparing characteristics between women who did and did not receive 17-OHPC during their pregnancy; 3) evaluating medication adherence to 17-OHPC; 4) identifying characteristics of those who were adherent versus non-adherent; 5) investigating associations between utilization and adherence status of 17-OHPC and the incidence of PTB in the real-world setting; and 6) determining if 17-OHPC utilization is associated with the incidence of GDM, GHT, or preeclampsia.

Chapter 3 Methods

3.1 Institutional Review Board Approval

This study was approved by The University of Texas at Austin Institutional Review Board. All data were in a de-identified form.

3.2 Objectives and Hypotheses

Generally, the aims of this study were to evaluate the utilization, adherence, and effectiveness of 17-OHPC among pregnant women at risk of preterm birth in a real-world setting. The specific objectives and hypotheses are listed below:

1) To describe characteristics of pregnant women with high PTB risk and utilization of 17-OHPC among eligible women;

2) To compare differences between high PTB risk pregnant women with and without 17-OHPC by their age group, insurance type, geographic region, pre-index diabetes, pre-index hypertension, pre-index Charlson comorbidity index (CCI) score, and pre-index diagnoses of alcohol, tobacco, or drug abuse;

2a) H_0: There is no significant difference in age between high PTB risk pregnant women with and without 17-OHPC.

H_1: There is significant difference in age between high PTB risk pregnant women with and without 17-OHPC.

2b) H_0: There is no significant difference in insurance type between high PTB risk pregnant women with and without 17-OHPC.

H_1: There is significant difference in insurance type between high PTB risk pregnant women with and without 17-OHPC.

2c) H_0: There is no significant difference in geographic region between high PTB risk pregnant women with and without 17-OHPC.

H_1: There is significant difference in geographic region between high PTB risk pregnant women with and without 17-OHPC.

2d) H_0: The initiation of 17-OHPC is not significantly related to whether pregnant women with high PTB risk had pre-index diabetes or not.

H_1: The initiation of 17-OHPC is significantly related to whether pregnant women with high PTB risk had pre-index diabetes or not.

2e) H_0: The initiation of 17-OHPC is not significantly related to whether pregnant women with high PTB risk had pre-index hypertension or not.

H_1: The initiation of 17-OHPC is significantly related to whether pregnant women with high PTB risk had pre-index hypertension or not.

2f) H_0: There is no significant difference in proportion of different pre-index CCI score between high PTB risk pregnant women with and without 17-OHPC.

H_1: There is significant difference in proportion of different pre-index CCI score between high PTB risk pregnant women with and without 17-OHPC.

2g) H_0: The initiation of 17-OHPC is not significantly related to whether pregnant women with high PTB risk had pre-index diagnoses of alcohol, tobacco, or drug abuse or not.

H_1: The initiation of 17-OHPC is significantly related to whether pregnant women with high PTB risk had pre-index diagnoses of alcohol, tobacco, or drug abuse or not.

3) To assess medication adherence of high PTB risk pregnant women receiving 17-OHPC;

4) To investigate the association between medication adherence and patients' age, insurance type, post-index diabetes, post-index hypertension, post-index CCI score, and post-index alcohol, tobacco, or drug abuse;

4a) H_0: There is no significant difference in age between high PTB risk pregnant women with and without adequate medication adherence.

H_1: There is significant difference in age between high PTB risk pregnant women with and without adequate medication adherence.

4b) H_0: There is no significant difference in insurance type between high PTB risk pregnant women with and without adequate medication adherence.

H_1: There is significant difference in insurance type between high PTB risk pregnant women with and without adequate medication adherence.

4c) H_0: There is no significant difference in proportion of post-index diabetes diagnoses between high PTB risk pregnant women with and without adequate medication adherence.

H_1: There is significant difference in proportion of post-index diabetes diagnoses between high PTB risk pregnant women with and without adequate medication adherence.

4d) H_0: There is no significant difference in proportion of post-index hypertension diagnoses between high PTB risk pregnant women with and without adequate medication adherence.

H_1: There is significant difference in proportion of post-index hypertension diagnoses between high PTB risk pregnant women with and without adequate medication adherence.

4e) H_0: There is no significant difference in proportion of different post-index CCI score between high PTB risk pregnant women with and without 17-OHPC.

H_1: There is significant difference in proportion of different post-index CCI score between high PTB risk pregnant women with and without 17-OHPC.

4f) H_0: There is no significant difference in proportion of post-index diagnoses of alcohol, tobacco, or drug abuse between high PTB risk pregnant women with and without 17-OHPC.

H_1: There is no significant difference in proportion of post-index diagnoses of alcohol, tobacco, or drug abuse between high PTB risk pregnant women with and without 17-OHPC.

5) To evaluate the association between the incidence of PTB and patients' age, insurance type, geographic region, post-index CCI score, and alcohol, tobacco, or drug abuse;

5a) H_0: There is no significant difference in age between high PTB risk pregnant women with and without PTB.

H_1: There is significant difference in age between high PTB risk pregnant women with and without PTB.

5b) H_0: There is no significant difference in insurance type between high PTB risk pregnant women with and without PTB.

H_1: There is significant difference in insurance type between high PTB risk pregnant women with and without PTB.

5c) H_0: There is no significant difference in geographic region between high PTB risk pregnant women with and without PTB.

H_1: There is significant difference in geographic region between high PTB risk pregnant women with and without PTB.

5d) H_0: There is no significant difference in proportion of post-index diabetes diagnoses between high PTB risk pregnant women with and without PTB.

H_1: There is significant difference in proportion of post-index diabetes diagnoses between high PTB risk pregnant women with and without PTB.

5e) H_0: There is no significant difference in proportion of post-index hypertension diagnoses between high PTB risk pregnant women with and without PTB.

H_1: There is significant difference in proportion of post-index hypertension diagnoses between high PTB risk pregnant women with and without PTB.

5f) H_0: There is no significant difference in proportion of different post-index CCI score between high PTB risk pregnant women with and without PTB.

H_1: There is significant difference in proportion of different post-index CCI score between high PTB risk pregnant women with and without PTB.

5g) H_0: There is no significant difference in proportion of post-index alcohol, tobacco, or drug abuse diagnoses between high PTB risk pregnant women with and without PTB.

H_1: There is significant difference in proportion of post-index alcohol, tobacco,

or drug abuse diagnoses between high PTB risk pregnant women with and without PTB.

6) To investigate the association between incidence of PTB and utilization and adherence status of 17-OHPC.

6a) H_0: There is no significant difference in PTB rate between high PTB risk pregnant women with and without 17-OHPC.

H_1: There is significant difference in PTB rate between high PTB risk pregnant women with and without 17-OHPC.

6b) H_0: There is no significant difference in PTB rate between high PTB risk pregnant women with and without adequate medication adherence.

H_1: There is significant difference in PTB rate between high PTB risk pregnant women with and without adequate medication adherence.

6c) H_0: There is no association between PTB rate and utilization and adherence status of high PTB risk pregnant women (non-17-OHPC users, adherers, non-adherers).

H_1: There is significant association between PTB rate and utilization and adherence status of high PTB risk pregnant women (non-17-OHPC users, adherers, non-adherers).

6d) H_0: There is no association between PTB rate and utilization and adherence status of high PTB risk pregnant women (non-17-OHPC users, adherers, non-adherers), controlling for other covariates (patients' age, insurance type, geographic region, post-index CCI score, and post-index diagnoses

of alcohol, tobacco, or drug abuse).

H_1: There is significant association between PTB rate and utilization and adherence status of high PTB risk pregnant women (non-17-OHPC users, adherers, non-adherers), controlling for other covariates (patients' age, insurance type, geographic region, post-index CCI score, and post-index diagnoses of alcohol, tobacco, or drug abuse).

7) To explore if incidence of diabetes (including GDM) or hypertension (including GHT and preeclampsia) is associated with utilization and adherence status of 17-OHPC.

7a) H_0: The use of 17-OHPC is not significantly associated with the incidence of diabetes.

H_1: The use of 17-OHPC is significantly associated with the incidence of diabetes.

7b) H_0: The adherence of 17-OHPC is not significantly associated with the incidence of diabetes.

H_1: The adherence of 17-OHPC is not significantly associated with the incidence of diabetes.

7c) H_0: The incidence of diabetes is not significantly associated with utilization and adherence status of 17-OHPC (non-17-OHPC users, adherers, non-adherers).

H_1: The incidence of diabetes is significantly associated with utilization and adherence status of 17-OHPC (non-17-OHPC users, adherers, non-adherers).

7d) H_0: The use of 17-OHPC is not significantly associated with the incidence of hypertension.

H_1: The use of 17-OHPC is significantly associated with the incidence of hypertension.

7e) H_0: The adherence of 17-OHPC is not significantly associated with the incidence of hypertension.

H_1: The adherence of 17-OHPC is significantly associated with the incidence of hypertension.

7f) H_0: The incidence of hypertension is not significantly associated with utilization and adherence status of 17-OHPC (non-17-OHPC users, adherers, non-adherers).

H_1: The incidence of hypertension is significantly associated with utilization and adherence status of 17-OHPC (non-17-OHPC users, adherers, non-adherers).

3.3 Study Design

This was a retrospective cohort study using a secondary database, the Decision Resources Group (DRG) claims database. The DRG database contains information from over 300 million patients and over 1.8 million health care providers in the U.S. Patients' demographic information (age, race, gender, geographic region), medical claims, and pharmacy claims were provided in the database. In terms of patient coverage by state, the highest medical claims coverage was in the Eastern U.S., with more than 60% coverage in Maryland, New Jersey, New York, Ohio, Pennsylvania, Maine, West Virginia, and Washington

DC. The pharmacy claims were concentrated in the center of the country, with more than a 46% capture in Kentucky, West Virginia, Ohio, and Michigan. In terms of health care providers' information, variables including national provider identifier, affiliation hierarchy, treatment settings (in-patient or out-patient), and line item charge details were included in the DRG database.

The data were drawn from the DRG claims database from January 1, 2012 to December 31, 2017. Women with a high risk of PTB, operationalized as having a history of PTB (see section 3.4.1), were included. The first diagnosis date of high-risk pregnancy for each patient was defined as the index date. The pre-index period was 6 months before the index date, and the pre-index period was necessary to guarantee the feasibility of evaluating the relationship between pre-index comorbidities and 17-OHPC utilization status. The patients were followed up until their delivery, which may happen during the 9 months after the index date. The study timeline is demonstrated by Figure 3.1. Information extracted from the DRG databases is listed in Table 3.1.

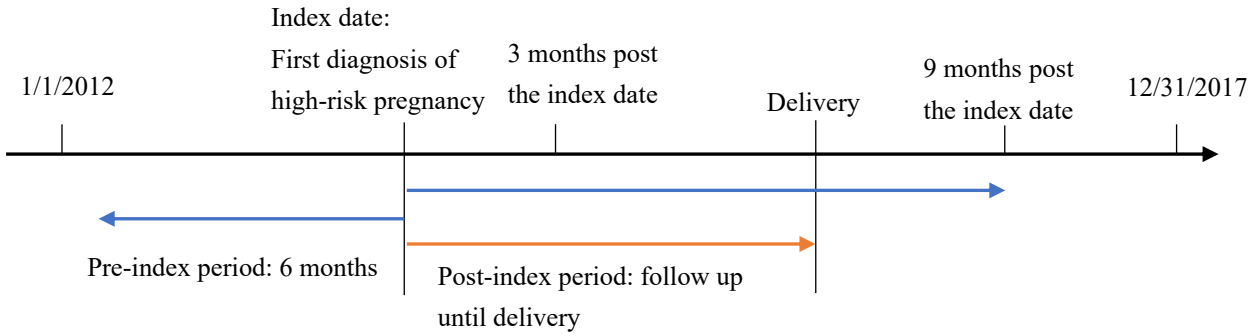


Figure 3. 1 Study Timeline

Table 3. 1 Decision Resources Group Database Variables Information

Variable name	Description
PATIENT_SUFFIX	Unique Patient Identifier
PATIENT_GENDER	Patient gender (M=male, F=female, U=unknown)
PATIENT_DOB	Patient's birth year
RACE	Racial profile of the Patient
ETHNICITY	Ethnic profile of the Patient
PRIMARY_DIAGNOSIS	The standard diagnosis codes associated with the claim based on the relevance to the encounter (primary diagnosis - reason for visit)
DIAGNOSIS_CODE_2	The standard diagnosis codes associated with the claim based on the relevance to the encounter, level 2
DIAGNOSIS_CODE_3	The standard diagnosis codes associated with the claim based on the relevance to the encounter, level 3
DIAGNOSIS_CODE_4	The standard diagnosis codes associated with the claim based on the relevance to the encounter, level 4
DIAGNOSIS_CODE_5	The standard diagnosis codes associated with the claim based on the relevance to the encounter, level 5
DIAGNOSIS_CODE_6	The standard diagnosis codes associated with the claim based on the relevance to the encounter, level 6
DIAGNOSIS_CODE_7	The standard diagnosis codes associated with the claim based on the relevance to the encounter, level 7
DIAGNOSIS_CODE_8	The standard diagnosis codes associated with the claim based on the relevance to the encounter, level 8
PROCEDURE	CPT/ HCPCS code
PROCEDURE_TYPE	ICD 9.10 procedure= ICD or HCPCS/CPT = CPT
NDC	National Drug Code
PLACE_SERVICE	HIPAA standard place of service code set
SERVICE_FROM	First date of service
SERVICE_TO	Last date of service
STATEMENT_FROM	First date of service for an inpatient stay
STATEMENT_TO	Last date of service for an inpatient stay
FACILITY_NPI	Facility National Provider Identifier
FACILITY_ADR_STATE	Facility State
FACILITY_ADR_CITY	Facility City
TYPE_COVERAGE	Payer type ID (commercial, Medicare, Medicaid etc.)
MIN_DIAG_DATE	First diagnosis date of preterm labor
DELIVERY_DATE	Delivery date of the Patient for that particular episode of Pregnancy
PROG_TREATED	Flag indicating whether the patient was treated with Progesterone therapy or not

3.4 Study Population

3.4.1 Population Inclusion Criteria

Patients were included if they met the following criteria: (a) female; (b) age≥16 years

and ≤50 years; (c) diagnoses of "Pregnancy with history of pre-term labor" or "Personal history of pre-term labor" based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), V23.41 and V13.21, and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM), O09.21 and Z87.51; (d) were continuously enrolled for at least 6 months before the index date; (e) and had a delivery date recorded. Only women aged ≥16 years and ≤50 years were included, because women who are younger than 16 years and who are older than 50 years face higher risks of PTB, and these groups only accounted for a small proportion of total sample.

3.4.2 Population Exclusion Criteria

Women were excluded if they: (a) had multiple gestations (ICD-9-CM: 651.xx, 652.xx, V31.xx, V32.xx, V33.xx, V34.xx, V35.xx, V36.xx, V37.xx; ICD-10-CM: O30.xx, O32.xx, Z37.2x, Z37.3x, Z37.4x, Z37.5x, Z37.6x, Z37.7x, Z38.3x, Z38.4x, Z38.5x, Z38.6x, Z38.7x, Z38.8x); (b) had cervical shortening (ICD-9-CM: 649.7x; ICD-10-CM: O26.87x); (c) had cervical cerclage (Current Procedural Terminology (CPT) code, 59320); and (d) the delivery took place within 3 months- or after 9 months- post the index date. If a woman's recorded delivery date is more than 9 months after the index date, it is probable that the delivery is the outcome of another pregnancy rather than the one that was used to identify the index date. Thus, they were excluded in this study. The women with a delivery date within 3 months after the index date were also excluded, because they may have seen the physician at a later gestational age, and even if 17-OHPC was initiated on the index date, they were less likely to receive at least 10 injections (prerequisite of adequate adherence) compared to other

patients. Since this may affect the evaluation of adherence and effectiveness of 17-OHPC, these women were also excluded.

3.5 Study Variables

3.5.1 Independent Variables

Independent variables included patients' age group, insurance type, geographic region, comorbidity (diabetes and hypertension), CCI, abuse of alcohol, tobacco or drugs, utilization and adherence status of 17-OHPC. The independent variables differ according to different study objectives.

For objective 1, the baseline demographic and clinical characteristics of included patients were described, which included age group, insurance type, geographic region, pre-index diabetes, pre-index hypertension, pre-index CCI, pre-index abuse of alcohol, tobacco, or drugs. The age groups consisted of ages: ≥16 and <20 years; ≥20 and <25 years; ≥25 and <30 years; ≥30 and <35 years; ≥35 and <40 years; and ≥40 and ≤50 years. Insurance type was categorized as Medicaid, commercial insurance plan, and others. Patients who were dually eligible for Medicaid and any other insurance were categorized as Medicaid patients. As for the comorbidities, since the billing guide of Makena indicated that physicians should be more vigilant when prescribing Makena for patients with a diagnosis of diabetes or hypertension,[99] if patients had diabetes or hypertension diagnoses recorded before the first high-risk pregnancy diagnosis date (i.e. index date), their chance of receiving 17-OHPC may be affected. Thus, the proportion of women with pre-index diabetes or hypertension was included. The pre-index CCI score and the proportion of the sample with a diagnosis of alcohol, tobacco, or drug abuse were also described in the objective 1. In addition, the post-index clinical characteristics of the

sample were also described, because they were compared in objective 4.

For objective 2, age group, insurance type, geographic region, pre-index diabetes, pre-index hypertension, pre-index CCI, and pre-index abuse of alcohol, tobacco, or drugs were compared among the 17-OHPC and non-17-OHPC cohorts.

For objectives 3 and 4, the independent variables included the baseline demographic characteristics (age group, insurance type) and the post-index clinical characteristics (diabetes, hypertension, CCI, and abuse of alcohol, tobacco, or drug). The post-index diabetes diagnoses included GDM; the post-index hypertension diagnoses included GHT and preeclampsia. These characteristics were compared among non-adherers and adherers. The post-index clinical characteristics were compared because some women may have gestational diabetes, gestational hypertension, or other maternal complications after the index date, and the adherence of 17-OHPC may be affected by both pre-index comorbidities and the conditions that were diagnosed during the post-index period (including comorbidities and maternal complications).

The independent variables for objective 5 were age group, insurance type, geographic region, post-index diabetes, post-index hypertension, post-index CCI, and post-index abuse of alcohol, tobacco, or drugs. The post-index clinical characteristics were applied here because the post-index comorbidities and maternal complications may better characterize a women's risk of having PTB than the pre-index clinical characteristics.

In objectives 6 and 7, the independent variable was the utilization and adherence status of 17-OHPC, specifically whether women were adherers, non-adherers, or non-17-OHPC users.

3.5.2 Dependent Variables

Dependent variables include utilization of 17-OHPC, medication adherence, incidence

of PTB, incidence of diabetes, and incidence of hypertension.

Whether patients used 17-OHPC or not is the dependent variables for objective 2. Being adherent or not adherent to 17-OHPC is the dependent variable for objectives 3 and 4. In terms of medication adherence measurement, since the guidelines suggested injections of 17-OHPC should start between 16-24 weeks and continue until 36 weeks or delivery, 10 weeks of injections was used as the preliminary cut-off for adequate adherence. In order to further calculate adherence, the number of days between the delivery date and the first claim date of 17-OHPC injection was calculated, and then was divided by 7 (ceil this number) to get the maximum number of weeks that patients were able to receive injections. For those with greater than or equal to 10 weeks of injection, if the received number of injections divided by the maximum number of weeks that patients should get injections is greater than 0.7, the patient was considered to be adherent to 17-OHPC; otherwise, the patient was considered nonadherent (Table 3.2). For example, if a woman initiated 17-OHPC at the 20th week of gestation and delivered at the 35th week of gestation, her adherence would be 100% if she received 16 injections. However, if she received 10 injections, then her adherence rate would be 62.5% (10 received injections out of 16 possible injections), and, thus, she would be treated as a non-adherer. If another woman initiated 17-OHPC at the 28th week of gestation and delivered at the 36th week of gestation, she would be treated as a non-adherer even if she received 9 injections out of 9 possible injections, because she did not initiate the drug in the recommended gestational window. In the sensitivity analysis, 10 weeks of injection was used as the cut-off for adequate adherence.

The dependent variable for objectives 5 and 6 was the incidence of PTB. The incidence

of diabetes (including GDM) and incidence of hypertension (including GHT or preeclampsia) were the dependent variables for objective 7.

Table 3. 2 Formula for Adherence Calculation

Adherent (Yes=1; No=0)	Calculation Formula
0	# of 17-OHPC < 10
0	# of 17-OHPC ≥ 10; and $\frac{\#\text{ of } 17-\text{OHPC injections}}{(\text{delivery date} - \text{first Rx date})/7} < 0.7$
1	# of 17-OHPC ≥ 10; and $\frac{\#\text{ of } 17-\text{OHPC injections}}{(\text{delivery date} - \text{first Rx date})/7} \geq 0.7$

** Ceil the denominator: (delivery date-first Rx date)/7*

3.5.3 Study Covariates

The available factors that could confound the relationship between the incidence of PTB and the utilization and adherence status of 17-OHPC were examined and controlled for in the study. For objective 6, age, insurance type, geographic region, post-index diabetes, post-index hypertension, post-index CCI, and post-index abuse of alcohol, tobacco, or drugs were used as covariates in the regression model.

All of the included variables and their operational definitions are summarized in Table 3.3.

Table 3. 3 Summary of Included Variables and Their Operational Definitions

Variables	Operational Definition
Age group	≥ 16 and < 20 years; ≥ 20 and < 25 years; ≥ 25 and < 30 years; ≥ 30 and < 35 years; ≥ 35 and < 40 years; ≥ 40 and ≤ 50 years
Insurance type	Medicaid Commercial insurance Others
Geographic region	Northeast region West region Southwest region Southeast region Midwest region
Pre-index diabetes	0 = no diabetes 1 = with diabetes
Pre-index hypertension	0= no hypertension 1= with hypertension
Pre-index CCI[a]	CCI score=0 CCI score=1 CCI score=2 CCI score≥3
Pre-index abuse of alcohol, tobacco or drug	0= no abuse of alcohol, tobacco or drug 1= with abuse of alcohol, tobacco or drug
Post-index diabetes (including GDM[b])	0 = no diabetes 1 = with diabetes
Post-index hypertension (including GHT[c] and preeclampsia)	0= no hypertension 1= with hypertension
Post-index CCI[a]	CCI score=0 CCI score=1 CCI score=2 CCI score≥3
Post-index abuse of alcohol, tobacco or drug	0= no abuse of alcohol, tobacco or drug 1= with abuse of alcohol, tobacco or drug
Use of 17-OHPC	0 = non-17-OHPC user 1 = 17-OHPC user
Medication adherence	0 = Not adherent 1 = Adherent
Utilization and adherence status of 17-OHPC	0 = non-17-OHPC user 1 = non-adherer 2 = adherer
Incidence of PTB[d]	0 = no PTB 1 = with PTB
Incidence of diabetes (including GDM[b])	0 = no diabetes 1 = with diabetes
Incidence of hypertension (including GHT[c] and preeclampsia)	0= no hypertension 1= with hypertension

[a] ***CCI= Charlson Comorbidity Index***

[b] ***GDM=Gestational diabetes***

[c] GHT=Gestational hypertension
[d] PTB=Preterm birth

3.6 Statistical Analyses

All statistical analyses were performed using SAS software v.9.4. An alpha level of 0.05 was used for all statistical analyses.

Descriptive statistics (i.e., mean, standard deviation, frequency) were used to summarize the baseline characteristics and post-index clinical characteristics of the sample in objective 1.

The proportion of the study population who were 17-OHPC or non-17-OHPC cohorts, and the proportion of 17-OHPC utilization by year were investigated in objective 2. Chi-square tests were conducted to evaluate the association between patients' use of 17-OHPC (yes/no) and their age, insurance type, geographic region, proportion of pre-index diabetes, proportion of pre-index hypertension, pre-index CCI, and proportion of pre-index alcohol, tobacco, or drug abuse.

The proportion of study cohorts who were adherent versus not adherent was described for objective 3. Chi-square tests were conducted for objective 4 to evaluate the association between patients' adherence of 17-OHPC (yes/no) and their age, insurance type, proportion of post-index diabetes, proportion of post-index hypertension, post-index CCI, and proportion of post-index alcohol, tobacco, or drug abuse.

Chi-square tests were also conducted for objective 5 to examine the association between the incidence of PTB (yes/no) and patients' age, insurance type, geographic region, post-index diabetes, post-index hypertension, post-index CCI, and proportion of post-index alcohol, tobacco, or drug abuse.

In objective 6, bivariate analyses (Chi-square tests) were conducted to evaluate the association between the incidence of PTB (yes/no) and use of 17-OHPC (yes/no), the association between the incidence of PTB (yes/no) and adherence of 17-OHPC (yes/no), as well as the association between the incidence of PTB (yes/no) and utilization and adherence status of 17-OHPC (non-users/non-adherers/adherers). The association between the incidence of PTB and utilization and adherence status of 17-OHPC (non-users/non-adherers/adherers) was also evaluated after controlling the covariates by conducting logistic regression analysis.

In objective 7, the aim was to investigate if use of 17-OHPC was associated with the incidence of diabetes or hypertension, and, thus, the proportion of patients with newly-diagnosed diabetes or hypertension after their initiation of 17-OHPC injection would be calculated. However, for the non-users cohort, it was impossible to use the 17-OHPC initiation date as the cut-off to calculate the proportion of newly diagnosed diabetes or hypertension patients. By checking the difference in days between the index day and the 17-OHPC initiation day, it was found that more than 95% of women initiated 17-OHPC on the index day. Therefore, the index date (first diagnoses for history of PTB) was used as the proxy for 17-OHPC initiation date. Chi-square tests were applied as well to investigate if 17-OHPC utilization and adherence was associated with the incidence of diabetes or hypertension after the index date.

Table 3.4 summarizes study objectives, their corresponding independent variables, dependent variables, covariates, and statistical tests.

Table 3. 4 Summary of Objectives, Study Variables, and Statistical Tests

Objectives	Dependent Variables	Independent Variables	Covariates	Statistical Analysis
1) To describe patients' baseline characteristics	N/A	N/A	N/A	Descriptive statistics (i.e. mean, standard deviation, frequency)
2) To describe 17-OHPC utilization and compare baseline characteristics by utilization status of 17-OHPC	Use of 17-OHPC (categorical)	Age group, insurance type, geographic region, pre-index diabetes, pre-index hypertension, pre-index CCI, pre-index abuse of alcohol, tobacco, or drug (categorical);	N/A	Chi-square test
3) To assess medication adherence of women receiving 17-OHPC	Adherence to 17-OHPC (categorical)	N/A	N/A	Descriptive statistics (i.e. mean, standard deviation, frequency)
4) To compare patients' characteristics by adherence status of 17-OHPC	Adherence to 17-OHPC (categorical)	Age group, insurance type, post-index diabetes, post-index hypertension, post-index CCI, and post-index abuse of alcohol, tobacco, or drug (categorical)	N/A	Chi-square test
5) To compare patients' characteristics by delivery outcome	Incidence of PTB (categorical)	Age group, insurance type, geographic region, post-index diabetes, post-index hypertension, post-index CCI, and post-index abuse of alcohol, tobacco, or drug (categorical)	N/A	Chi-square test;

Table 3. 4 (continued)

Objectives	Dependent Variables	Independent Variables	Covariates	Statistical Analysis
6) To compare delivery outcome by utilization and adherence status of 17-OHPC	Incidence of PTB (categorical)	Utilization and adherence status of 17-OHPC (categorical)	Age group, insurance type, geographic region, post-index diabetes, post-index hypertension, post-index CCI, and post-index abuse of alcohol, tobacco. or drug (categorical)	Chi-square test; Logistic regression
7) To determine if utilization and adherence status 17-OHPC is related to incidence of diabetes or hypertension	Incidence of diabetes (including GDM), incidence of hypertension (including GHT and preeclampsia) (categorical)	Utilization and adherence status of 17-OHPC (categorical)	N/A	Chi-square test

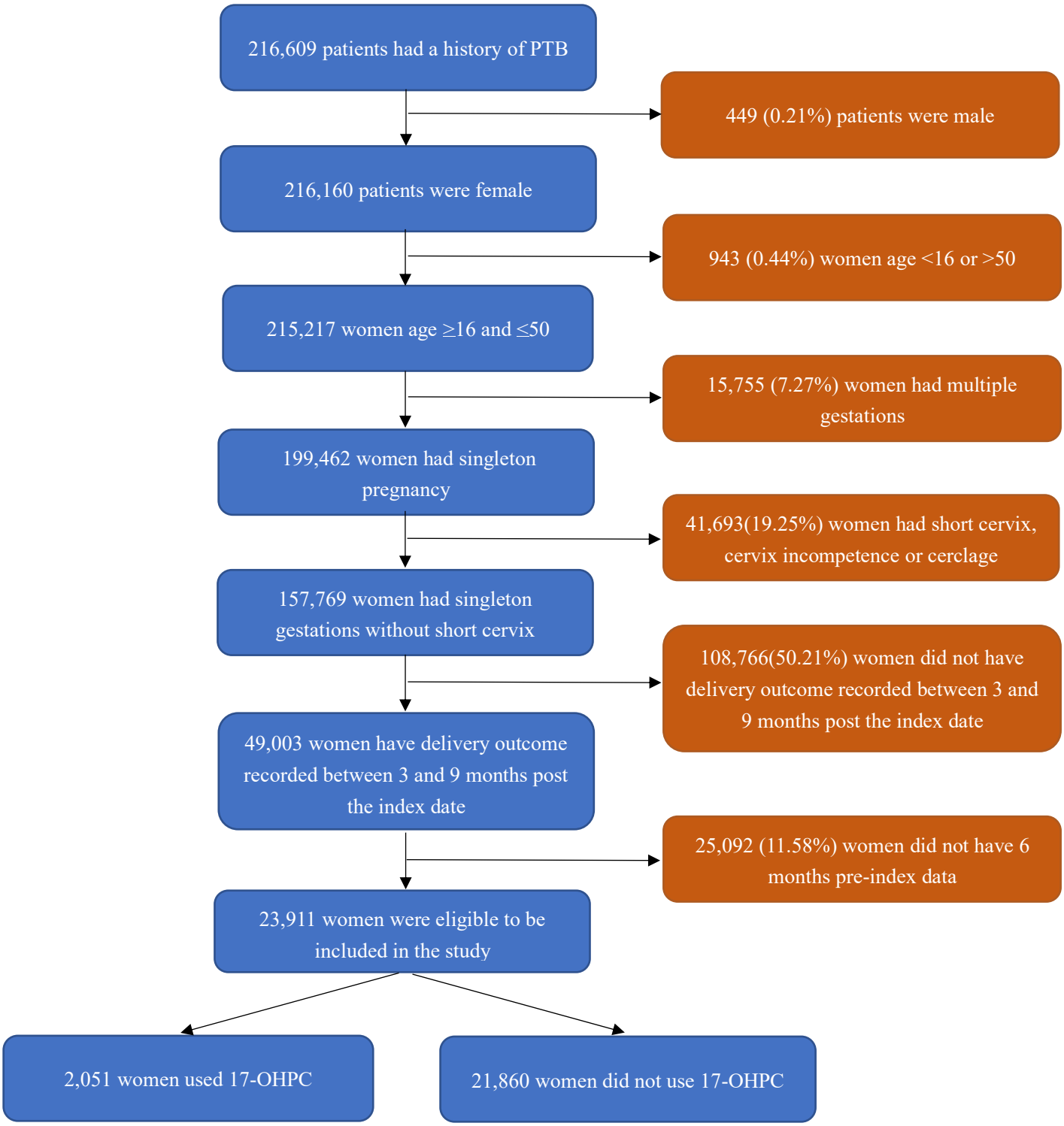
Chapter 4 Results

This chapter provides a detailed description of the study results, including the sample attrition process and other results, which are presented in the corresponding order of study objectives outlined in Chapter 3.

4.1 Sample Selection

Initially, data for 216,609 patients were included from the Decision Resource Group (DRG) database, with at least one diagnosis code of "supervision of high-risk pregnancy, with history of pre-term labor." A small proportion of patients may share insurance with their husbands or other family members, which potentially resulted in some patients' gender shown in the claims databases as male. After excluding patients with "male" gender in the database, 216,160 female patients were left. When including women between 16 and 50 years, 215,217 were left in the cohort. Furthermore, since 17-OHPC was not shown to be effective for women with multiple gestations, and its efficacy for women with short cervix was inconclusive, 15,755 women with multiple gestations, and 41,693 women with short cervix, cervix incompetence, or receiving cerclage surgery were excluded from the sample. To evaluate the adherence and effectiveness of 17-OHPC, it is necessary to make sure that each patient had delivery outcomes recorded in the database, and the delivery took place between 3 months and 9 months after their index date. In addition, a 6-month pre-index period was applied. After all criteria were applied 23,911 women were eligible to be included in this study. The patient attrition process is shown in Figure 4.1.

Figure 4. 1 Patient Attrition Flowchart in DRG databases



4.2 Description of Patients' Demographic and Clinical Characteristics

The mean age for the sample was 29.3 (SD 5.6) years of age. Patient age was sorted into 7 groups, with a 5-year range for each group. Approximately 60% of the sample was between 25 and 34 years old, while only 2.16% were between 16 and 20, and 3.82% were between 40 and 50. The insurance types were categorized into Medicaid, commercial insurance, and 'other' insurance. The other insurance category included Medicare, CHAMPUS, self-pay, etc. Patients enrolled in commercial insurance accounted for 64.49% of the total sample, followed by Medicaid patients (32.66%). In terms of the race/ethnicity, 84.12% of patients had missing race/ethnicity coding, and, thus, the bivariate analysis was not conducted for the relationship between 17-OHPC utilization and race/ethnicity. Since the geographic distribution of patients covered by the DRG database was unequal, the high-risk pregnant women included in this study were also unequally distributed in different areas. Patients residing in the Southwest U.S. accounted for a large proportion of the sample (34.34%), which was followed by the Midwest (24.46%), Northwest (15.71%), Southwest (10.05%), and West (6.19%) regions.

In addition to the demographic characteristics, patients' baseline clinical characteristics were also examined. The sample had a mean CCI score of 0.54 (SD 0.78), with 61.34% having no comorbidities. Diagnoses indicating patients with issues of alcohol, tobacco, or drug abuse were also analyzed, and 14.79% of the sample had at least one of the three conditions. A summary of the sample's demographic and baseline clinical characteristics is presented in Table 4.1.

Table 4. 1 Demographic and Baseline Clinical Characteristics of the Sample

Baseline Characteristics		Number (n=23,911)	Percent (%)
Age group	Mean±SD	29.34±5.58	
	16-19	516	2.16
	20-24	4,714	19.71
	25-29	7,304	30.55
	30-34	6,834	28.58
	35-39	3,629	15.18
	40-50	914	3.82
Insurance type	Medicaid	7,810	32.66
	Commercial	15,467	64.49
	Others	634	2.65
Race/Ethnicity	White	2,463	10.30
	Asian	81	0.34
	Black	999	4.18
	Hispanic or Latino	152	0.64
	Other	102	0.43
	Null/Missing	20,114	84.12
Geographic region	Northeast	3,756	15.71
	Midwest	5,847	24.46
	West	1,479	6.19
	Southeast	8,211	34.34
	Southwest	2,404	10.05
	Null/Missing	2,212	9.25
Diabetes	Yes	1,307	5.47
	No	22,604	94.53
Hypertension	Yes	2,578	10.78
	No	21,333	89.22
CCI[a]	Mean±SD	0.54±0.78	
	0	14,667	61.34
	1	6,333	26.49
	2	2,186	9.14
	≥3	725	3.03
Alcohol, tobacco, or drug abuse	Yes	3,537	14.79
	No	20,374	85.21

[a] *CCI= Charlson Comorbidity Index*

The post-index clinical characteristics of the sample were described in Table 4.2. Post-index diabetes included type I diabetes, type II diabetes, and gestational diabetes (GDM); and 9.7% of the sample had diagnoses of diabetes after the index date. Post-index hypertension included normal hypertension, gestational hypertension (GHT), and preeclampsia; and 20% of the sample had diagnoses of hypertension after the index date. Compared to the baseline mean

CCI score, the post-index CCI score was higher, which was 0.92 (SD 1.02). The proportion of patients without any comorbidity decreased from 61.34% to 42.83%, and the proportion of patients with at least three comorbidities increased from 3.03% to 7.79%.

Table 4. 2 Description of Post-index Clinical Characteristics of the Sample

Clinical Variables		Number (n=23,911)	Percent (%)
Diabetes [a]	Yes	2,322	9.71
	No	21,589	90.29
Hypertension [b]	Yes	4,974	20.80
	No	18,937	79.20
CCI [c]	Mean±SD	0.92±1.02	
	0	10,240	42.83
	1	7,896	33.06
	2	3,913	16.36
	≥3	1,862	7.79
Alcohol, tobacco, or drug abuse	Yes	4,962	20.75
	No	18,949	79.25

[a] *Gestational diabetes was included*

[b] *Gestational hypertension and preeclampsia were included*

[c] *CCI= Charlson Comorbidity Index*

4.3 Utilization of 17-OHPC

4.3.1 Utilization Rate of 17-OHPC

Among 23,911 women with a singleton delivery outcome who were eligible to use of 17-OHPC, less than ten percent (2,051 (8.58%)) had least one claim for 17-OHPC. When the utilization rate was examined by the index year, we found the utilization rate showed an increasing trend, from 5.58% in 2012 to 21.97% in 2017 (Table 4.3).

Table 4. 3 Utilization Rate of 17-OHPC by Year

Index Year	Number of 17-OHPC Users	Number of eligible 17-OHPC Users	Percent of 17-OHPC Utilization (%)
2012	15	269	5.58
2013	318	5,497	5.78
2014	689	9,412	7.32
2015	573	5,868	9.76
2016	260	1,973	13.18
2017	196	892	21.97
TOTAL 2012-2017	2,051	23,911	8.58

4.3.2 Comparison of Baseline Characteristics by 17-OHPC Utilization Status

The mean age for 17-OHPC users and non-17-OHPC users was 29.38 years old and 29.33 years old, respectively. Given that patients under 20 and those above 35 only accounted for a small proportion of the total sample, patients with age 16-19 and 20-24 were merged into one group. Similarly, patients with ages equal to or over 35 years were merged into one age group. The chi-square test result showed that there was no relationship between patients' age and their utilization status of 17-OHPC ($p=0.33$). Nonetheless, the utilization rate showed an increasing tendency with the increase of patients' age among patients with age from 16 to 34. The utilization rates for patients aged 16-24, 25-29, and 30-34 were 8.08%, 8.79%, and 8.90%, respectively. However, the rate decreased slightly for women who were 35 and above.

In terms of the relationship between insurance type and 17-OHPC utilization status, a significant difference in the 17-OHPC utilization rate was observed. Compared to the utilization rate among patients enrolled in Medicaid (7.16%) and commercial insurances (9.17%), the "Others" group had the highest utilization rate (11.51%). The reason for the high utilization rate in the 'Other' category was further investigated; and it was noted that patients with CHAMPUS (renamed TRICARE) insurance had a much higher utilization rate (33.73%) than women with other insurance plans. By further examining the national provider identifiers

of patients with CHAMPUS insurance, it was found that the majority of 17-OHPC injections were prescribed by two providers from the same state. It is possible that these two providers highly support the use of 17-OHPC. If the utilization rate was only compared between patients with Medicaid and commercial insurances, patients with commercial insurances were shown to be higher utilizers of 17-OHPC ($p<0.0001$).

The utilization rate of 17-OHPC was shown to be significantly different for women in different areas of the US ($p<0.0001$). The highest utilization rate was 12.65% in the Southwest area, following by 9.95% in the Midwest area, and the lowest utilization rate in the Northeast area (4.61%).

The association between 17-OHPC utilization and patients' comorbidities was also examined. A total of 1,307 (5.5%) patients had a diagnosis for diabetes before the index date. Patients with a pre-index diagnosis for diabetes accounted for 5.47% of non-17-OHPC users and 5.41% of 17-OHPC users. A total of 2,578 (10.78%) patients were diagnosed with hypertension before the index date; 10.87% of non-17-OHPC users had diagnoses of hypertension, which seemed to be slightly higher than that among 17-OHPC users (9.85%). However, neither pre-index diabetes ($p=0.91$) nor pre-index hypertension ($p=0.15$) diagnoses were found to be related with patients' use of 17-OHPC. Moreover, the utilization rate was shown to be unrelated with the CCI score ($p=0.42$). Additionally, patients without a diagnosis for abuse of tobacco, alcohol, or drugs were more likely to use 17-OHPC (8.73%) than women with these conditions (7.72%) ($p=0.048$).

The comparison of patients' baseline characteristics by 17-OHPC utilization is summarized in Table 4.4.

Table 4. 4 Comparison of Baseline Characteristics by Utilization Status of 17-OHPC

Baseline Characteristics	Non-17-OHPC Users (N, %) (n=21,860)	17-OHPC Users (N, %) (n=2,051)	*p* Value [a]
Age group			0.33
16-24	4,809 (22.00)	421 (20.53)	
25-29	6,662 (30.48)	642 (31.30)	
30-34	6,226 (28.48)	608 (29.64)	
≥ 35	4,163 (19.04)	380 (18.53)	
Insurance type			**<0.0001**
Medicaid	7,251 (33.17)	559 (27.25)	
Commercial	14,048 (64.26)	1,419 (69.19)	
Others	561 (2.57)	73 (3.56)	
Geographic region			**<0.0001**
Northeast	3,583 (16.39)	173 (8.43)	
Midwest	5,267 (24.09)	582 (28.38)	
West	1,365 (6.24)	114 (5.56)	
Southeast	7,562 (34.59)	649 (31.64)	
Southwest	2,100 (9.61)	304 (14.82)	
Null/Missing	1,983 (9.07)	229 (11.17)	
Diabetes			0.91
Yes	1,196 (5.47)	111 (5.41)	
No	20,664 (94.53)	1,940 (94.59)	
Hypertension			0.15
Yes	2,376 (10.87)	202 (9.85)	
No	19,484 (89.13)	1,849 (90.15)	
CCI [b]			0.42
0	13,412 (61.35)	1,255 (61.19)	
1	5,799 (26.53)	534 (26.04)	
2	1,980 (9.06)	206 (10.04)	
≥3	669 (3.06)	56 (2.73)	
Alcohol, tobacco, or drug abuse			**0.048**
Yes	3,264 (14.93)	273 (13.31)	
No	18,596 (85.07)	1,778 (86.69)	

[a] *p values were determined by cross-tabulations with chi square analysis, significant at p<0.05 (in bold)*

[b] *CCI=Charlson Comorbidity Index*

4.4 Medication Adherence

4.4.1 Evaluation of Medication Adherence

Of the 2051 women prescribed 17-OHPC, 407 (19.84%) were adherent using our definition of adherence. Patients were considered to be adherent if they received ≥10 injections, and their number of injections divided by the maximum number of weeks recommended was greater than 0.7. The average number of injections the patients received was 7.50 (SD 6.01). A sensitivity analysis using a less stringent definition of medication adherence was also conducted. In the sensitivity analysis, patients receiving no less than 10 injections were categorized as adherers. Under this definition, 686 (33.45%) of users were adherent to 17-OHPC.

4.4.2 Comparison of Patients' Characteristics by 17-OHPC Adherence Status

In order to investigate if patients' characteristics were associated with their adherence, bivariate analyses and the corresponding sensitivity analyses were conducted. The base case results and sensitivity analysis results are summarized in Table 4.5 and Table 4.6. The adherence rates were 16.63%, 20.40%, 20.23%, and 21.84% for women aged 16-24, 25-29, 30-34, and ≥ 35 years old. No significant difference was found between adherence rate and age (p=0.27). A similar trend was also observed in the sensitivity analysis, with adherence rates of 32.30%, 32.24%, 33.39%, and 36.84% for women aged 16-24, 25-29, 30-34, and ≥ 35 years old. Similarly, there was no significant difference (p=0.45).

The adherence rate was significantly different for patients with different insurance plans; 21.29% of Medicaid patients, 18.32% of commercial insurance patients, and 38.36% of patients with other insurances were adherent to 17-OHPC. Similar to the high utilization rate shown in

the “Others” group, CHAMPUS patients had a high adherence rate (59.22%) as well, which increased the overall adherence rate of the “Others” group. When the comparison was made between Medicaid patients and patients enrolled in commercial insurances, even though Medicaid patients had a higher adherence rate, there was no statistically significant difference (p=0.13). Again, in the sensitivity analysis using the second definition of adherence, patients in the “Other” group were most adherent, with a 47.95% adherence rate. However, Medicaid patients were significantly more likely to be adherent (37.57%) than commercial insurance patients (31.08%) (p=0.01).

In terms of the association between patients’ post-index comorbidities and adherence, no relationship was found between adherence to 17-OHPC and diabetes (p=0.63), hypertension (p=0.84), or CCI score (p=0.82). No significant difference was found in any sensitivity analyses as well. The adherence rate for patients with tobacco, alcohol, or drug abuse diagnoses was mathematically lower than those without these conditions (16.20% vs. 20.61%). However, there was no statistically significant difference using the original definition (p=0.06), nor the second definition of adherence (p=0.65).

Table 4. 5 Comparison of Patients' Characteristics by Adherence of 17-OHPC

Patients' Characteristics	Nonadherent 17-OHPC Users (N, %) (n=1,644)	Adherent 17-OHPC Users (N, %) (n=407)	*p* Value [a]
Age group			0.27
16-24	351 (21.35)	70 (17.20)	
25-29	511 (31.08)	131 (32.19)	
30-34	485 (29.50)	123 (30.22)	
≥ 35	297 (18.07)	83 (20.39)	
Insurance type			**<0.0001**
Medicaid	440 (26.76)	119 (29.24)	
Commercial	1,159 (70.50)	260 (63.88)	
Others	45 (2.74)	28 (6.88)	
Diabetes [b]			0.63
Yes	167 (10.16)	47 (11.55)	
No	1,477 (89.84)	360 (88.45)	
Hypertension [c]			0.84
Yes	343 (20.86)	87 (21.38)	
No	1,301 (79.14)	320 (78.62)	
CCI [d]			0.82
0	728 (44.28)	190 (46.68)	
1	523 (31.81)	127 (31.21)	
2	272 (16.55)	63 (15.48)	
≥3	121 (7.36)	27 (6.63)	
Alcohol, tobacco, or drug abuse			0.06
Yes	300 (18.25)	58 (14.25)	
No	1,344 (81.75)	349 (85.75)	

[a] p values were determined by cross-tabulations with chi square analysis, significant at p<0.05 (in bold)

[b] Gestational diabetes was included

[c] Gestational hypertension and preeclampsia were included

[d] CCI=Charlson Comorbidity Index

** Adherence definition: Patients received ≥ 10 injections, and their number of injections divided by the maximum number of weeks recommended was greater than 0.7*

Table 4. 6 Sensitivity Analyses of Comparison of Patients' Characteristics by Adherence of 17-OHPC

Patients' Characteristics	Nonadherent 17-OHPC Users (N, %) (n=1,365)	Adherent 17-OHPC Users (N, %) (n=686)	*p* Value [a]
Age group			0.45
16-24	285 (20.88)	136 (19.83)	
25-29	435 (31.87)	207 (30.17)	
30-34	405 (29.67)	203 (29.59)	
≥ 35	240 (17.58)	140 (20.41)	
Insurance type			**0.0006**
Medicaid	349 (25.57)	210 (30.61)	
Commercial	978 (71.65)	441 (64.29)	
Others	38 (2.78)	35 (5.10)	
Diabetes [b]			0.86
Yes	135 (9.89)	79 (11.52)	
No	1,230 (90.11)	607 (88.48)	
Hypertension [c]			0.38
Yes	293 (21.47)	137 (19.97)	
No	1,072 (78.53)	549 (80.03)	
CCI [d]			0.78
0	603 (44.18)	315 (45.92)	
1	442 (32.38)	208 (30.32)	
2	220 (16.12)	115 (26.76)	
≥3	100 (7.32)	48 (7.00)	
Alcohol, tobacco, or drug abuse			0.65
Yes	242 (17.73)	116 (16.91)	
No	1,123 (82.27)	570 (83.09)	

[a] p values were determined by cross-tabulations with chi square analysis, significant at p<0.05 (in bold)

[b] Gestational diabetes was included

[c] Gestational hypertension and preeclampsia were included

[d] CCI=Charlson Comorbidity Index

** Adherence definition: patients received ≥10 injections.*

4.5 PTB and 17-OHPC Utilization

Patients' baseline characteristics were compared by their delivery outcome (whether they had a PTB or not). The results are shown in Table 4.7. It is noted that except for post-index diabetes (p=0.3), the other characteristics were all shown to be associated with whether the women have PTB or not. In terms of age, the PTB rate for women aged 16-24, 25-29, 30-34, and ≥ 35 years old were 16.39%, 14.14%, 12.36%, and 11.64%, respectively, which suggested

that younger women, especially women younger than 25 years, were more likely to have a PTB ($p<0.0001$). Women with Medicaid insurance were more likely to have a PTB than those with commercial and other insurances ($p<0.0001$). The geographic region was also associated with PTB ($p<0.0001$), with the Northeast area showing the highest PTB rate (15.55%), followed by the Southeast area (13.93%) and the Southwest area (13.48%). Patients diagnosed with hypertension ($p=0.0006$), patients with a higher CCI score ($p<0.0001$), and those diagnosed with alcohol, tobacco, or drug abuse conditions ($p=0.002$) were also shown to be associated with higher PTB rate.

Table 4. 7 Comparison of Patients' Characteristics by Delivery Outcome

Patients' Characteristics	No PTB (N, %) (n=20,647)	PTB (N, %) (n=3,264)	*p* Value [a]
Age group			**<0.0001**
16-24	4,373 (21.18)	857 (26.26)	
25-29	6,271 (30.37)	1,033 (31.65)	
30-34	5,989 (29.01)	845 (25.89)	
≥ 35	4,014 (19.44)	529 (16.21)	
Insurance type			**<0.0001**
Medicaid	6,668 (32.30)	1,142 (34.99)	
Commercial	13,398 (64.89)	2,069 (63.39)	
Others	581 (2.81)	53 (1.62)	
Geographic region			**<0.0001**
Northeast	3,172 (15.36)	584 (17.89)	
Midwest	5,062 (24.52)	787 (24.11)	
West	1,289 (6.24)	190 (5.82)	
Southeast	7,067 (34.23)	1,144 (35.05)	
Southwest	2,080 (10.07)	324 (9.93)	
Null/Missing	1,977 (9.58)	235 (7.20)	
Diabetes			0.3022
Yes	2,037 (9.64)	285 (9.07)	
No	18,610 (90.36)	2,979 (90.93)	
Hypertension			**0.0006**
Yes	4,250 (20.11)	724 (22.73)	
No	16,397 (78.89)	2,540 (77.27)	
CCI [b]			**<0.0001**
0	8,952 (43.36)	1,288 (39.46)	
1	6,815 (33.01)	1,081 (33.12)	
2	3,314 (16.05)	599 (18.35)	
≥3	1,566 (7.58)	296 (9.07)	
Alcohol, tobacco, or drug abuse			**0.0023**
Yes	4,219 (20.43)	743 (22.76)	
No	16,428 (79.57)	2,521 (77.24)	

[a] *p values were determined by cross-tabulations with chi square analysis, significant at p<0.05 (in bold)*
[b] *CCI=Charlson Comorbidity Index*

Chi-square tests were conducted to investigate the association between use of 17-OHPC and PTB rate, as well as the relationship between 17-OHPC adherence and PTB rate. The results are presented in Table 4.8 and Table 4.9. The PTB rate was lower among non-17-OHPC users (13.61%) than 17-OHPC users (14.04%). However, no significant difference was found between the use of 17-OHPC and PTB rate (p=0.59). Among 17-OHPC users, the PTB rate

was higher among adherers than non-adherers (15.48% vs. 13.69%), but this was not statistically different (p=0.35). Since the covariates were not controlled in the bivariate analysis, 17-OHPC users and especially those adherent users may be determined to be at higher risk at the index date than those who did not use 17-OHPC. The comparison of the PTB rate was also made among non-users, adherent users, and non-adherent users (p=0.55), and the results are presented in Table 4.10.

Table 4. 8 Comparison of PTB Rate by Utilization Status of 17-OHPC

PTB	Non-17-OHPC Users (N, %) (n=21,860)	17-OHPC Users (N, %) (n=2,051)	*p* Value [a]
Yes	2,976 (13.61)	288 (14.04)	0.59
No	18,884 (86.39)	1,763 (85.96)	

[a] p values were determined by cross-tabulations with chi square analysis, significant at p<0.05

Table 4. 9 Comparison of PTB Rate by Adherence Status of 17-OHPC

PTB	Nonadherent 17-OHPC Users (N, %) (n=1,644)	Adherent 17-OHPC Users (N, %) (n=407)	*p* Value [a]
Yes	225 (13.69)	64 (15.48)	0.35
No	1,419 (86.31)	344 (84.52)	

[a] p values were determined by cross-tabulations with chi square analysis, significant at p<0.05
** Adherence definition: patients received ≥10 injections, and their received number of injections divided by the maximum number of weeks that patients should get injections is greater than 0.7*

Table 4. 10 Comparison of PTB Rate by Utilization and Adherence Status of 17-OHPC

PTB	Non-17-OHPC Users (N, %) (n=21,860)	Nonadherent 17-OHPC Users (N, %) (n=1,644)	Adherent 17-OHPC Users (N, %) (n=407)	*p* Value [a]
Yes	2,976 (13.61)	255 (13.69)	63 (15.48)	0.55
No	18,884 (86.39)	1,419 (86.31)	344 (84.52)	

[a] p values were determined by cross-tabulations with chi square analysis, significant at p<0.05
** Adherence definition: patients received ≥10 injections, and their received number of injections divided by the maximum number of weeks that patients should get injections is greater than 0.7*

In the sensitivity analysis using the alternative definition of adherence, there is still no difference in PTB rate found between adherers and non-adherers (p=0.35). Using this less

stringent way to define medication adherence, we found very similar rates of PTB between adherers (13.99%) and non-adherers (14.07%) (See Table 4.11 and Table 4.12).

Table 4. 11 Sensitivity Analysis of Comparison of PTB Rate by Utilization and Adherence Status of 17-OHPC

PTB	Nonadherent 17-OHPC Users (N, %) (n=1,365)	Adherent 17-OHPC Users (N, %) (n=686)	*p* Value [a]
Yes	192 (14.07)	96 (13.99)	0.96
No	1,173 (85.93)	590 (86.01)	

[a] *p values were determined by cross-tabulations with chi square analysis, significant at p<0.05*

** Adherence definition: patients received ≥10 injections.*

Table 4. 12 Sensitivity Analysis of Comparison of PTB Rate by Utilization and Adherence Status of 17-OHPC

PTB	Non-17-OHPC Users (N, %) (n=21,860)	Nonadherent 17-OHPC Users (N, %) (n=1,365)	Adherent 17-OHPC Users (N, %) (n=686)	*p* Value [a]
Yes	2,976 (13.61)	192 (14.07)	96 (13.99)	0.86
No	18,884 (86.39)	1,173 (85.93)	590 (86.01)	

[a] *p values were determined by cross-tabulations with chi square analysis, significant at p<0.05*

** Adherence definition: patients received ≥10 injections.*

A logistic regression was also conducted to investigate the relationship between the utilization and adherence status of 17-OHPC and the incidence of PTB. The results showed that there is still no significant difference in PTB rate between non-17-OHPC users and non-adherent users (OR=1.04, 95% CI=0.90-1.20), and adherent users (OR=1.26, 95% CI=0.96-1.65) after controlling the covariates. Holding the other covariates constant, older patients aged 25-29, 30-35, and ≥35 were 17% (OR=0.83, 95% CI=0.72-0.92), 28% (OR=0.72, 95% CI=0.64-0.79), and 34% (OR=0.66, 95% CI=0.59-0.74) less likely to have PTB than patients aged <25, respectively; patients residing in the Southeast area were 12% less likely to have PTB (OR=0.88, 95% CI=0.79-0.98) than Northeast patients; patients with hypertension were 15% (OR=1.15, 95% CI=1.02-1.29) more likely to have PTB; patients with CCI of 1, 2, or ≥3

were 10% (OR=1.10, 95% CI=1.01-1.20), 26% (OR=1.26, 95% CI=1.14-1.41), and 35% (OR=1.35, 95% CI=1.17-1.56) more likely to have PTB than patients with CCI of 0. However, no significant difference in the incidence of PTB was observed between patients with commercial insurance and Medicaid patients (OR=0.95, 95% CI=0.87-1.03), between patients with and without diabetes (OR=1.17, 95% CI=1.00-1.38), and between patients with and without diagnoses of alcohol, tobacco, or drug abuse (OR=1.04, 95% CI=0.95-1.14). The results are shown in Table 4.13.

Table 4. 13 Logistic Regression of Incidence of PTB by Patients' Utilization and Adherence Status of 17-OHPC

Variables	OR	95% CI	Wald X_2	*p* Value [a]
Utilization and adherence status of 17-OHPC				
Non-adherent users	1.04	0.90-1.20	0.58	0.4451
Adherent users	1.26	0.96-1.65	2.18	0.1402
Covariates				
Age				
25-29	0.83	0.72-0.92	2.45	0.1175
30-35	0.72	0.64-0.79	9.49	0.0021
≥35	0.66	0.59-0.74	22.16	<0.0001
Insurance type				
Commercial	0.95	0.87-1.03	8.84	0.0030
Others	0.56	0.42-0.75	14.05	0.0002
Geographic region				
Midwest	0.82	0.73-0.92	0.01	0.9201
West	0.81	0.68-0.97	0.01	0.9064
Southeast	0.88	0.79-0.98	4.02	0.0450
Southwest	0.80	0.69-0.93	0.14	0.7138
Null/Missing	0.64	0.54-0.75	16.44	<0.0001
Diabetes	1.17	1.00-1.38	3.93	0.0475
Hypertension	1.15	1.02-1.29	5.04	0.0247
CCI				
CCI=1	1.10	1.01-1.20	3.87	0.0493
CCI=2	1.26	1.14-1.41	3.97	0.0464
CCI≥3	1.35	1.17-1.56	7.94	0.0048
Alcohol, tobacco, or drug abuse	1.04	0.95-1.14	0.74	0.3892

[a] p values were determined by cross-tabulations with chi square analysis, significant at p<0.05
OR=odds ratio; CI=confidence interval; X_2=Chi-square; CCI=Charlson Comorbidity Index
Reference categories: non-17-OHPC users; aged <=25; Medicaid insurance; Northeast geographic region; CCI=0; With diagnoses of alcohol, tobacco or drug abuse

4.6 Incidence of Diabetes and Hypertension and 17-OHPC Utilization

The relationship between 17-OHPC utilization and the incidence of diabetes (including GDM) and hypertension (including GHT and preeclampsia) were investigated using chi-square tests. In this case, the patients with new diagnoses of diabetes or hypertension after the index date were included in the analysis. The results are summarized in Table 4.14, showing that 5.68% of non-users and 5.02% of users had a post-index diagnosis of diabetes with no pre-index code for the condition. No significant association was found between 17-OHPC utilization and incidence of new diabetes diagnosis (p=0.21). In terms of the incidence of hypertension, 13.08% of non-users and 11.12% of users were newly diagnosed with hypertension after the index date. Furthermore, 17-OHPC users were significantly less likely to have a new hypertension diagnosis than the non-users (p=0.01).

Table 4. 14 Relationship Between 17-OHPC Utilization and Incidence of Diabetes or Hypertension

Maternal Complication	Non-17-OHPC Users (N, %) (n=21,860)	17-OHPC Users (N, %) (n=2,051)	*p* Value [a]
Diabetes [b]			0.21
Yes	1,242 (5.68)	103 (5.02)	
No	20,618 (94.32)	1,948 (94.98)	
Hypertension [c]			**0.01**
Yes	2,859 (13.08)	228 (11.12)	
No	19,001 (86.92)	1,823 (88.88)	

[a] *p values were determined by cross-tabulations with chi square analysis, significant at p<0.05 (in bold)*
[b] *Gestational diabetes was included*
[c] *Gestational hypertension and preeclampsia were included*

The association between 17-OHPC adherence and incidence of diabetes or hypertension was also examined. Among adherers, 5.65% were newly diagnosed with diabetes and 11.79% were newly diagnosed with hypertension, both of which are higher than that for non-adherers, with 4.87% newly diagnosed with diabetes and 10.95% newly diagnosed with

hypertension (See Table 4.15). However, adherence of 17-OHPC was not found to be significantly related to incidence of diabetes (p=0.52), nor incidence of hypertension (p=0.62). No significant difference was found in the sensitivity analyses as well (See Table 4.16).

Table 4. 15 Relationship Between 17-OHPC Adherence and Incidence of Diabetes or Hypertension

Maternal Complication	Nonadherent 17-OHPC Users (N, %) (n=1,644)	Adherent 17-OHPC Users (N, %) (n=407)	*p* Value[a]
Diabetes [b]			0.52
Yes	80 (4.87)	23 (5.65)	
No	1,564 (95.13)	384 (94.35)	
Hypertension [c]			0.62
Yes	180 (10.95)	48 (11.79)	
No	1,464 (89.05)	359 (88.21)	

[a] p values were determined by cross-tabulations with chi square analysis, significant at p<0.05

[b] Gestational diabetes was included

[c] Gestational hypertension and preeclampsia were included

** Adherence definition: patients received ≥10 injections, and their received number of injections divided by the maximum number of weeks that patients should get injections is greater than 0.7*

Table 4. 16 Sensitivity Analysis of Relationship Between 17-OHPC Adherence and Incidence of Diabetes or Hypertension

Maternal Complication	Nonadherent 17-OHPC Users (N, %) (n=1,365)	Adherent 17-OHPC Users (N, %) (n=686)	*p* Value[a]
Diabetes [b]			0.16
Yes	62 (4.54)	41 (5.98)	
No	1,303 (95.46)	645 (94.02)	
Hypertension [c]			0.85
Yes	153 (11.21)	75 (10.93)	
No	1,212 (88.79)	611 (10.93)	

[a] p values were determined by cross-tabulations with chi square analysis, significant at p<0.05

[b] Gestational diabetes was included

[c] Gestational hypertension and preeclampsia were included

** Adherence definition: patients received ≥10 injections.*

When the incidence rate of diabetes was compared among non-users, adherent users, and non-adherent users, no association was found between use of 17-OHPC and incidence of diabetes in both the base case (p=0.38) and the sensitivity analysis (p=0.19). As for

hypertension, the use of 17-OHPC was associated with a lower incidence rate of hypertension (p=0.04). However, the result may not indicate a 'practical' difference from the clinical point of view. The results were shown in Table 4.17 and 4.18.

Table 4. 17 Relationship Between Utilization and Adherence Status of 17-OHPC and Incidence of Diabetes or Hypertension

Maternal Complication	Non-17-OHPC Users (N, %) (n=21,860)	Nonadherent 17-OHPC Users (N, %) (n=1,644)	Adherent 17-OHPC Users (N, %) (n=407)	*p* Value [a]
Diabetes [b]				0.38
Yes	1,242 (5.68)	80 (4.87)	23 (5.65)	
No	20,618 (94.32)	1,564 (95.13)	384 (94.35)	
Hypertension [c]				**0.04**
Yes	2,859 (13.08)	180 (10.95)	48 (11.79)	
No	19,001 (86.92)	1,464 (89.05)	359 (88.21)	

[a] p values were determined by cross-tabulations with chi square analysis, significant at p<0.05 (in bold)

[b] Gestational diabetes was included

[c] Gestational hypertension and preeclampsia were included

** Adherence definition: patients received ≥10 injections, and their received number of injections divided by the maximum number of weeks that patients should get injections is greater than 0.7*

Table 4. 18 Sensitivity Analysis of Relationship Between Utilization and Adherence Status of 17-OHPC and Incidence of Diabetes or Hypertension

Maternal Complication	Non-17-OHPC Users (N, %) (n=21,860)	Nonadherent 17-OHPC Users (N, %) (n=1,365)	Adherent 17-OHPC Users (N, %) (n=686)	*p* Value [a]
Diabetes [b]				0.19
Yes	1,242 (5.68)	62 (4.54)	41 (5.98)	
No	20,618 (94.32)	1,303 (95.46)	645 (94.02)	
Hypertension [c]				**0.04**
Yes	2,859 (13.08)	153 (11.21)	75 (10.93)	
No	19,001 (86.92)	1,212 (88.79)	611 (89.07)	

[a] p values were determined by cross-tabulations with chi square analysis, significant at p<0.05 (in bold)

[b] Gestational diabetes was included

[c] Gestational hypertension and preeclampsia were included

** Adherence definition: patients received ≥10 injections.*

A summary of study objectives, hypotheses, statistical tests, and corresponding results is presented in Table 4.19.

Table 4. 19 Summary of Objectives, Hypotheses, and Testing Results

Objectives	Hypotheses	Statistical Analysis	Testing Results
1) To describe patients' baseline characteristics	N/A	Descriptive statistics (i.e. mean, standard deviation, frequency)	N/A
2) To describe 17-OHPC utilization, and compare baseline characteristics by utilization status of 17-OHPC	H_{02a}: There is no significant difference in age between high PTB risk pregnant women with and without 17-OHPC.	Chi-square test;	Failed to reject
	H_{02b}: There is no significant difference in insurance type between high PTB risk pregnant women with and without 17-OHPC.		Rejected
	H_{02c}: There is no significant difference in geographic region between high PTB risk pregnant women with and without 17-OHPC.		Rejected
	H_{02d}: The initiation of 17-OHPC is not significantly related to whether pregnant women with high PTB risk had pre-index diabetes or not.		Failed to reject
	H_{02e}: The initiation of 17-OHPC is not significantly related to whether pregnant women with high PTB risk had pre-index hypertension or not.		Failed to reject
	H_{02f}: There is no significant difference in proportion of different pre-index CCI score between high PTB risk pregnant women with and without 17-OHPC.		Failed to reject
	H_{02g}: The initiation of 17-OHPC is not significantly related to whether pregnant women with high PTB risk had pre-index diagnoses of alcohol, tobacco, or drug abuse or not.		Rejected
3) To assess medication adherence of women receiving 17-OHPC	N/A	Descriptive statistics (i.e. mean, standard deviation, frequency)	N/A

Table 4. 19 (continued)

Objectives	Hypotheses	Statistical Analysis	Testing Results
4) To compare patients' characteristics by adherence status of 17-OHPC	H_{04a}: There is no significant difference in age between high PTB risk pregnant women with and without adequate medication adherence.	Chi-square test;	Failed to reject
	H_{04b}: There is no significant difference in insurance type between high PTB risk pregnant women with and without adequate medication adherence.		Rejected
	H_{04c}: There is no significant difference in proportion of post-index diabetes between high PTB risk pregnant women with and without adequate medication adherence.		Failed to reject
	H_{04d}: There is no significant difference in proportion of post-index hypertension between high PTB risk pregnant women with and without adequate medication adherence.		Failed to reject
	H_{04e}: There is no significant difference in proportion of different post-index CCI score between high PTB risk pregnant women with and without 17-OHPC.		Failed to reject
	H_{04f}: There is no significant difference in proportion of post-index diagnoses of alcohol, tobacco, or drug abuse between high PTB risk pregnant women with and without 17-OHPC.		Failed to reject

Table 4.19 (continued)

Objectives	Hypotheses	Statistical Analysis	Testing Results
5) To compare patients' characteristics by delivery outcome	H_{05a}: There is no significant difference in age between high PTB risk pregnant women with and without PTB.	Chi-square test	Rejected
	H_{05b}: There is no significant difference in insurance type between high PTB risk pregnant women with and without PTB.		Rejected
	H_{05c}: There is no significant difference in geographic region between high PTB risk pregnant women with and without PTB.		Rejected
	H_{05d}: There is no significant difference in proportion of post-index diabetes diagnoses between high PTB risk pregnant women with and without PTB		Failed to reject
	H_{05e}: There is no significant difference in proportion of post-index hypertension diagnoses between high PTB risk pregnant women with and without PTB		Rejected
	H_{05f}: There is no significant difference in proportion of different post-index CCI score between high PTB risk pregnant women with and without PTB.		Rejected
	H_{05g}: There is no significant difference in proportion of post-index alcohol, tobacco, or drug abuse diagnoses between high PTB risk pregnant women with and without PTB.		Rejected

Table 4.19 (continued)

Objectives	Hypotheses	Statistical Analysis	Testing Results
6) To compare delivery outcome by utilization and adherence status of 17-OHPC	H_{06a}: There is no significant difference in PTB rate between high PTB risk pregnant women with and without 17-OHPC.	Chi-square test;	Failed to reject
	H_{06b}: There is no significant difference in PTB rate between high PTB risk pregnant women with and without adequate medication adherence.		Failed to reject
	H_{06c}: There is no association between PTB rate and utilization and adherence status of high PTB risk pregnant women (non-17-OHPC users, adherers, non-adherers).		Failed to reject
	H_{06d}: There is no association between PTB rate and utilization and adherence status of high PTB risk pregnant women (non-17-OHPC users, adherers, non-adherers), controlling for covariates.	Logistic regression	Failed to reject
7) To determine if utilization and adherence status 17-OHPC is related to incidence of diabetes (including GDM) or hypertension (including GHT or preeclampsia).	H_{07a}: The use of 17-OHPC is not significantly associated with the incidence of diabetes.	Chi-square test	Failed to reject
	H_{07b}: The adherence of 17-OHPC is not significantly associated with the incidence of diabetes.		Failed to reject
	H_{07c}: The incidence of diabetes is not significantly associated with utilization and adherence status of 17-OHPC (non-17-OHPC users, adherers, non-adherers).		Failed to reject
	H_{07d}: The use of 17-OHPC is not significantly associated with the incidence of hypertension.		Rejected
	H_{07e}: The adherence of 17-OHPC is not significantly associated with the incidence of hypertension.		Failed to reject
	H_{07f}: The incidence of hypertension is not significantly associated with utilization and adherence status of 17-OHPC (non-17-OHPC users, adherers, non-adherers).		Rejected

Chapter 5 Discussion

5.1 Chapter Overview

This chapter provides a review of the study purpose and a detailed discussion of the study results for each objective. Possible explanations of the results and comparisons with results of a Texas Medicaid database analysis and other studies are provided. The strengths and limitations of the study are also discussed in this chapter. Lastly, the major conclusions and recommendations for future studies are provided.

5.2 Study Purpose

The main purpose of this study was to investigate the utilization, adherence, and effectiveness of 17-OHPC. Patients' characteristics that may be associated with 17-OHPC utilization and adherence status were investigated, which included age, insurance type, geographic region, comorbidities, and tobacco, alcohol, or drug abuse. The relationships between 17-OHPC utilization and incidence of maternal complications, including gestational diabetes (GDM), gestational hypertension (GHT), and preeclampsia were also examined in the study.

5.3 Study Objectives

5.3.1 Objective 1 and 2: Utilization of 17-OHPC and patients' characteristics

In this study, less than ten percent (8.58%) of women at risk for recurrent PTB who met criteria received 17-OHPC from 2012 to 2017. This number is higher than that was reported by the Louisiana Department of Health and Hospitals (4.67% in 2011 and 7.41% in 2013).[110] However, the utilization rates in the DRG database increased each year, from 5.58% of eligible women in 2012, to 7.32% in 2014, which is consistent with that among Louisiana Medicaid patients. The utilization rate in the DRG cohort continued to increase to 9.76% in 2015, 13.18% in 2016, and 21.97% in 2017, which may reflect a growing trend in its use. By applying the same inclusion and

exclusion criteria, similar objectives were also investigated among Texas Medicaid cohorts from July 1, 2013 to June 30, 2015. The patient attrition process for this analysis is shown in Appendix Figure A.1. In the Texas Medicaid database, we found that 585 out of 3,541 eligible women (16.52%) used 17-OHPC (unpublished internal report). Although the utilization rate in Texas Medicaid was higher than the average utilization rate of DRG cohorts, it should be noted that the average utilization rate in the Southwest area (12.65%) of the DRG cohort was shown to be the highest across the country. In addition, this number is consistent with the findings of Cross-Barnet et al. (2018). This study was conducted by the Center for Medicare and Medicaid Innovation, which launched Strong Start programs from 2013 to 2017, and 27 awardees from over 200 sites in 30 states participated. They reported that 14.95% of 45,999 eligible enrolled patients received 17-OHPC.[135]

Generally, the utilization rate of 17-OHPC is still low, and factors that may be associated with utilization rates were investigated. According to our results, among the investigated demographic and clinical characteristics, age and medical comorbidities were not associated with the use of 17-OHPC. This is consistent with other studies. Similar results were found in the Texas Medicaid database, as neither patients' age (p=0.39) nor their race/ethnicity (p=0.14) was related to 17-OHPC utilization (See Appendix Table A.1 and Table A.2). No association between the use of 17-OHPC and patients' medical comorbidities was reported in DeNoble et al.'s study either.[115]

Patients' insurance type, geographic region, and alcohol, tobacco, or drug abuse were shown to be related to the use of 17-OHPC. In terms of patients' insurance type, patients with commercial insurance were more likely to use 17-OHPC than Medicaid patients. This finding is consistent with Berhie et al.'s study, which found that women enrolled in public insurance were less likely to have 17-OHPC prescribed than privately insured patients (aOR = 0.39, 95% CI =

0.19-0.82).[120] One possible reason for the low utilization rate among public insurance patients is the administrative burden of preauthorization. Preauthorization is often required when 17-OHPC is prescribed, and, thus, women who were indecisive about the intervention or who initiated prenatal care late in their pregnancy may be further delayed by this extra step.[120] From a provider's perspective, different insurance plans have different processes and protocols of prior approval, which can consume a large amount of a prescriber's time. Thus, they may prefer to write a prescription for vaginal progesterone instead of spending time initiating an application for preauthorization.[135] Thus, variations in Medicaid and other insurance policies regarding the coverage and reimbursement of 17-OHPC may still be a barrier to patient access.[108]

In addition to insurance hurdles, other reported factors that were not included in the DRG database but have been previously associated with 17-OHPC underutilization included women's earliest PTB at greater gestational age,[115,136] delay in prenatal care initiation,[115,135] and Hispanic ethnicity.[115] Barriers of 17-OHPC uptake were also explored by qualitative studies from both the patient and provider perspectives. From the patient perspectives, the main barriers included unknown complications, concerns about safety, lack of information, time commitment, unstable housing, lack of childcare, and job inflexibility.[120,136] As for time commitment, patients were bothered more by the length of individual appointments, instead of the weekly injection routine.[136] Other provider-perceived barriers to patients' receipt of 17-OHPC included "financial barriers," "fear of injections," and "difficulty in arranging injections."[137] From the provider perspective, "the cost risks to provider," "'non-physician providers' practice scope limitations," and "the time-consuming preauthorization application process" are thought to be major barriers to prescribing 17-OHPC.[135] In addition, "concerns about neonatal untoward effects" and the "high cost of Makena" were pointed out in another online survey as barriers to prescribing 17-OHPC.[138] The

initial acquisition cost of branded 17-OHPC (Makena) was set at $1440 per injection; thus, the total cost for 20 injections would be about $30,000 per pregnancy.[139]

Facilitators of 17-OHPC utilization were also explored, including a universal insurance authorization process, options for home administration, and effective communication between patients and providers.[135] In addition, the active role of state and territorial health agencies in promoting the access and use of 17-OHPC is an important facilitator. Four main approaches that have been suggested are: 1) use databases to promote early identification of eligible women; 2) simplify the ordering process; 3) reimburse a woman's transportation to clinic appointments or offer home injections; and 4) inform providers and patients about the efficacy of 17-OHPC and clarify the reimbursement policies.[109] Several states, including Louisiana, North Carolina, Ohio, Texas, Iowa, and South California, are taking various approaches to promote the utilization of 17-OHPC, which may explain why the utilization rate of 17-OHPC is higher in the Southwest, Midwest, and Southeast regions of the U.S.

5.3.2 Objective 3 and 4: 17-OHPC Adherence and patients' characteristics

Two definitions were applied to evaluate patients' adherence to 17-OHPC in this study. By defining patients with at least 10 injections and 70% of their possible maximum number of injections as the minimum threshold, the adherence rate was 19.84%, which is close to the adherence rate of the Texas Medicaid cohort (18.97%), when applying the same adherence definition. In the sensitivity analysis, a less strict criterion was applied (patients receiving at least 10 injections were considered to be adherent), and the adherence rate was still only 33.45% among the DRG cohort and 29.40% among the Texas Medicaid cohort, both lower than that reported in other studies. However, it is noteworthy that no consistent definition was applied to evaluate 17-OHPC adherence across different studies. Studies reporting a high adherence rate usually had a

small sample size of patients from an individual medical institution. Yee et al. reported an 83% adherence rate with a sample size of 229 from a single institution.[113] DeNoble et al. reported a 72.2% adherence rate with sample size of 115 patients from a Duke University-affiliated hospital.[115]

Compared to studies using data from a single institution, the adherence rate was lower among studies using state Medicaid databases and national databases. With a sample size of 169, an adherence rate of 66.3% among the Massachusetts Medicaid population was reported by Hydery et al.[117] The adherence rate was 50% for a Louisiana Medicaid population with a larger sample size of 745, by defining adherence as receiving at least ten injections (the same as the adherence definition in the sensitivity analysis).[110] By using data collected from one of Centene's managed Medicaid programs, Lucas et al. found that 58.6% of 790 patients initiated 17-OHPC in the recommended gestational age window.[116] Carter et al. used MarketScan data and the adherence was measured similarly to our base case adherence analysis. The results showed that of 3,374 patients, 32.3% had an adherence rate over 85%, which is closer to what was reported in this study.[114] The higher adherence rate reported in studies using data from a single institution may be attributable to a higher quality of care received by patients with these providers. On the other hand, policies related to 17-OHPC reimbursement and prior authorization processes vary across different states. Thus, greater differences in population characteristics and variance in policies exist in the national databases compared to one certain individual state Medicaid database and one single medical institution.

In terms of factors related to adherence, only insurance type was found to be associated with a patients' adherence to 17-OHPC in this study. However, the significant difference is attributable to high adherence rate in the "others" group (38.36%). By further examining the

difference in adherence rates between patients with Medicaid or commercial insurance, no significant difference was observed. Similarly, Sutton et al. did not find a relationship between adherence and insurance status.[119] The other characteristics examined in the study, including age, geographic regions, and comorbidities, were not shown to be associated with adherence. For Texas Medicaid cohorts, no relationship between adherence and age or race was observed (See Appendix Table A.3 and Table A.4). Similarly, race, number of comorbidities, and different types of comorbidities were not shown to be associated with adherence in Hydery et al.'s study.[117] Carter et al. found that except for number of prior PTBs, the other factors, including maternal age and different types of comorbidities, were not shown to be related to the timing of 17-OHPC initiation.[114] However, maternal age was reported to be associated with adherence in several studies. DeNoble et al., Sutton et al., and Haidar et al. found that women with older maternal age were more likely to be adherent to 17-OHPC.[115,118,119] In our study, even though no statistically significant association was observed between adherence and age, the adherence rates showed an increasing trend for women aged 16-24, 25-29, 30-34, and ≥ 35 years old, with adherence rate of 16.63%, 20.40%, 20.23%, and 21.84%, respectively. It is possible that younger women have more access barriers to health care than older women, or may not be skilled enough to navigate the health care system.[115] In terms of race and ethnicity, Berhie et al.[120] and Yee et al.[113] stated that non-Hispanic Black women were less likely to be adherent than White women. The Texas Medicaid database analysis also showed that the adherence rate among White women (22.58%) was higher than that among Black women (18.33%) and Hispanic women (16.18%), although these differences were not statistically significant, and the variable indicating ethnicity was missing for the majority of patients.

Therefore, from the variables that were available from the DRG database, only age was

previously shown to possibly be associated with patients' adherence, although there is no consensus. Other factors that may affect patients' adherence were also investigated by a qualitative study or a study using mixed methodologies. Several barriers that were not available in the claims database might explain low adherence rates for 17-OHPC. First, some people fear injections, so after the first injection, patients may choose to stop receiving them.[110] Secondly, perfect adherence would consist of approximately 20 continuous injections or more. Such a long-term injection timeframe is burdensome for pregnant women. Despite home injections being available, not all insurance plans cover this option, so some pregnant women would need to go to their clinic every week. Thus, the long-term transportation and time commitment may be a burden that can reduce adherence.[110] Corresponding to this, two facilitators for participants' adherence were mentioned in previous research: administration location flexibility, and a well-designed work flow among entities involved in 17-OHPC provision, administration, and payment.[135] Additionally, the high cost may prevent people with low socioeconomic status or those with high insurance co-pays from being adherent.

5.3.3 Objective 5 and 6: Effectiveness of 17-OHPC

The PTB rate was not found to be associated with utilization and adherence status of 17-OHPC in this study. In the Texas Medicaid cohort, 17-OHPC users, especially the adherent users, were more likely to have PTB (p=0.003) (See Appendix Table A.5). However, covariates were not controlled in this case, so patients using 17-OHPC may be at higher risk of PTB than non-users. Our study results are consistent with the findings reported by Turitz et al.'s cross-sectional study[122] and Nelson et al.'s prospective cohort study.[98] Furthermore, the latest phase 3B RCT of 17-OHPC (PROLONG, NCT01004029) was completed in 2018, which did not demonstrate a statistically difference in the incidence of PTB between the treatment and placebo group (p=0.72).[101,102] The

researchers indicated that additional subgroup analyses of the PROLONG data were going to be conducted, especially focusing on patients with the highest risk of preterm delivery.[102]

However, a few previous studies showed the efficacy of 17-OHPC in preventing PTB or prolonging pregnancy duration. One probable reason for the contradiction is that patients using the drug, and especially those who were adherent to the drug, may have been at a higher risk of PTB than other patients, but the covariates available in the DRG database could not be used to determine the level of risk in order to control for it. DeNoble et al. found that patients who initiated prenatal care earlier in pregnancy, whose earliest prior PTB occurred at an earlier gestational age, and who experienced more PTBs were more likely to use 17-OHPC. Patients with these characteristics may be at a higher risk; however, these variables were unavailable in the claims database, so they could not be assessed. Our study was also limited to examining the incidence of PTB as the outcome of 17-OHPC; the gestational duration was not available and thus could not be evaluated. Among studies evaluating the effectiveness of 17-OHPC by examining the duration of pregnancy, even though they reported a longer gestational duration in the treatment group, women in that group may still experience PTB according to the definition of PTB (≤37 weeks of gestation). For example, Bastek et al. reported the gestational duration of 33.1 weeks in the treatment group versus 31.6 weeks in the control group.[123] Thus, if the rates of PTB were evaluated in these studies as the outcome of 17-OHPC, they may find no significant difference in PTB rate between two groups.

From this perspective, although the promotion of the utilization of 17-OHPC has been ongoing, uptake by prescribers may be slow because the effectiveness of 17-OHPC for prevention of SPTB reported by observational studies is still controversial, plus the newest clinical trial showed no efficacy of 17-OHPC. Thus, more studies are needed to confirm if 17-OHPC is effective in preventing recurrent SPTB, and clinicians should be cautious when prescribing 17-OHPC.

5.3.4 Objective 7: 17-OHPC Utilization and Incidence of Diabetes or Hypertension

The utilization of 17-OHPC was not found to be associated with the incidence of diabetes (including GDM) in this study. A similar result was observed in Texas Medicaid cohorts (p=0.70) (See Appendix Table A.6). The consistent result was also reported in a clinical trial conducted by Rouholamin et al.[130] Gyamfi et al. also arrived at a similar conclusion. They conducted a secondary analysis of 2 double-blind RCTs with 441 patients having singleton and 653 having twin gestations, and no association was found in either singleton or twin pregnancies.[128]

Although some studies found an association between 17-OHPC and a higher risk for GDM, we need to note the difference in patients' characteristics. Egerman et al. indicated that "in obese women with age greater than 35 years, earlier initiation of 17-OHPC may increase the risk for GDM."[129] Rebarber et al. found that for patients with similar maternal BMI and age, the incidence of GDM was higher for women receiving 17-OHPC.[125] However, a commentary relating to this article was published and pointed out that some covariates (e.g., ethnicity) were not considered in this study. In addition, selection bias may have existed since no explanation was given of the criteria used to select women for treatment.[140] It is also noteworthy that the two studies reporting the positive association were observational studies, while the studies reporting no association were conducted based on clinical trial data. Thus, it is possible that some covariates were unavailable or not controlled in the observational studies. This limitation commonly exists in retrospective cohort studies, which may weaken the strength of conclusions.

As for the relationship between 17-OHPC utilization and the incidence of hypertension (including GHT and preeclampsia), although the Makena billing guide listed GHT and preeclampsia as possible maternal complications of Makena based on the results from a clinical trial (8.8% in the treatment group versus 4.6% in the control group),[75,99] our results showed patients

receiving 17-OHPC were less likely to be newly diagnosed with hypertension (p=0.01), though the difference was not observed between adherers and non-adherers (p=0.62). This is consistent with results reported by Sammour et al.[131] and Amaral et al.,[133] which were mentioned in the literature review. However, no significant difference was observed in Ngai et al.'s study[132] and the Texas Medicaid cohorts, though both showed the incidence rate of hypertension was lower among users compared with non-users (Appendix Table A.6). Thus, whether 17-OHPC can be used for GHT or preeclampsia treatment or not still needs to be further confirmed by large scale clinical trials and more studies.

5.4 Study Strengths and Limitations

5.4.1 Study Strengths

This study used a nationwide claims database to investigate the utilization, adherence, and effectiveness of 17-OHPC. As pointed out in the literature review, most published research with similar aims as this study was either prospective cohort research or retrospective research based on one state Medicaid claims database or the electronic medical records (EMR) database of a single medical institution, where the sample size was usually small (less than 500) and the generalizability of the results was limited. In contrast, the sample size of this study was large, and the sample included women from different geographic regions. Thus, the results are more generalizable. Additionally, the utilization rate by geographic region can be compared.

Secondly, this study covered a 6-year timeframe (Jan 1st, 2012 – Dec 31st, 2017), which is a longer study period than that of other studies (usually 2-3 years), and this makes it feasible to examine the utilization trends of 17-OHPC over multiple years.

Thirdly, a reasonable approach of adherence evaluation was applied in this study, by referring to the guidelines and literature and using different methods of adherence measurement.

Sensitivity analysis using two methods of estimating medication adherence was conducted in the study.

Lastly, the available covariates were used to control for confounders when evaluating the association between utilization and adherence status of 17-OHPC and incidence of SPTB.

5.4.2 Study Limitations

This was a retrospective cohort study using the DRG claims database, so the research scope is limited by the information provided in the database. Inaccurate and inappropriate coding problems caused by human error may limit the accuracy of the research results. These limitations should be kept in mind when interpreting the results.

In objective 2, the specific codes for pharmacy-compounded 17-OHPC were not available, so only patients receiving FDA approved 17-OHPC were considered to be 17-OHPC users. Thus, the utilization rate of 17-OHPC may be underestimated. In addition, for objective 2 and objective 4, some patients' characteristics that may affect the utilization and adherence of 17-OHPC were not included in the claims database. For example, records of race were missing for more than 60% of the patients, so race differences in 17-OHPC utilization and adherence were not compared. Other important characteristics that may affect the chance of receiving and being adherent to 17-OHPC (e.g., BMI, number of prior PTBs, number of prior term births, gestational age at initiation of prenatal care, gestation duration of the prior PTB) were not available in the DRG database. For objective 2b and 4b, differences in patients' insurance types were compared between women with and without 17-OHPC, and between adherers and non-adherers. It is possible that some patients were covered by more than one insurance plan type (e.g., Medicaid and Blue Cross Blue Shield). If a patient was enrolled in both Medicaid and a commercial insurance plan, her insurance type was categorized as Medicaid, which may increase the proportion of women with Medicaid

receiving 17-OHPC.

As for the medication adherence assessment in objective 3, home injections of 17-OHPC cannot be confirmed in the database, so the analysis of adherence was limited to those who received in-office injections, which may result in the underestimation of adherence rates.

When evaluating the outcome of 17-OHPC in objective 6, the duration of pregnancy was intended to be used to measure the effectiveness of 17-OHPC. However, women may not see a practitioner early in their pregnancy, and it was impossible to obtain their pregnancy dates from the claims databases, so we were unable to evaluate the patients' duration of pregnancy as an outcome of 17-OHPC. Patients may get their first high-risk pregnancy diagnosis at any time during their gestation, so it is also inappropriate to use the index date as the proxy for the date of becoming pregnant. Thus, only the incidence of PTB (yes or no) was used as the outcome to evaluate the effectiveness of 17-OHPC. In addition, almost half of the patients' records of delivery date were "NULL/Missing," due to miscarriage, abortion, missing data, or other reasons. As a result, only women with delivery date records were included to assess the outcome of 17-OHPC, which may result in overestimation of the effectiveness of 17-OHPC. Simultaneously, some covariates indicating women might be at a higher risk of PTB were not available and unable to be controlled for in the analysis, and the women at a higher risk may be more likely to use 17-OHPC, so the effectiveness of 17-OHPC may be underestimated.

In objective 7, we explored whether the use of 17-OHPC was associated with the incidence of diabetes (including GDM) or hypertension (including GHT and preeclampsia). Patients with an initial diagnosis date of diabetes or hypertension before and after their first injection of 17-OHPC needed to be separated. However, for the non-user group, the first 17-OHPC injection date did not exist. Thus, the index date (diagnosis of risk of PTB) was used as the proxy date of the first

injection date of 17-OHPC, given that over 95% of included patients received their first injection on the index date. What is more, GDM and diabetes, as well as GHT and hypertension, should be better differentiated in this case. However, the DRG database contained both ICD-9-CM and ICD-10-CM codes. Although ICD-10-CM data provide individual codes for GDM and GHT, ICD-9-CM data only has codes for "diabetes complicating pregnancy, childbirth, or the puerperium, delivered, antepartum condition" and "hypertension complicating pregnancy, childbirth, or the puerperium, delivered, antepartum condition,"[141] without specific codes for GDM and GHT. Thus, the association between 17-OHPC utilization and incidence of GDM, GHT, or preeclampsia could not be assessed, but instead the association between 17-OHPC utilization and incidence of diabetes (including GDM) and hypertension (including GHT and preeclampsia) were examined in this study. In addition, it was assumed that patients without diagnosis codes of diabetes or hypertension during the pre-index period did not have the disease, so some patients with pre-index diabetes or hypertension might not have been identified if they had either diagnosis more than 6-months previously.

5.5 Conclusions and Recommendations for Future Research

5.5.1 Conclusions

To conclude, 17-OHPC utilization showed an increasing trend from 2012 to 2017, but it is still underutilized. The insurance type and geographic region were associated with the use of 17-OHPC. Patients with commercial insurance and patients residing in the Southwest region of the U.S. were more likely to use 17-OHPC. The adherence of 17-OHPC was low. No significant difference in adherence rate was found among women with different age groups, CCI, comorbidities (diabetes and hypertension), or abuse of alcohol, tobacco, or drugs. The SPTB rate was not found to be associated with utilization and adherence status of 17-OHPC. In terms of the

association between 17-OHPC and maternal complications, the use of 17-OHPC was not associated with GDM. However, the use of 17-OHPC was shown to be associated with a lower incidence of GHT or preeclampsia. Nonetheless, this may not indicate a 'practical' difference from the clinical point of view.

Since the effectiveness of 17-OHPC for prevention of SPTB is still being debated, more studies are needed to confirm if 17-OHPC is effective in preventing recurrent SPTB, and specifically identify women who are at a higher risk and possibly more likely to benefit from 17-OHPC.

5.5.2 Recommendations for Future Research

In the future, more research is needed to confirm the effectiveness of 17-OHPC in preventing SPTB and identifying specific populations that more likely to benefit from 17-OHPC. As for investigations of effectiveness of 17-OHPC in real-world settings, large-scale multicenter prospective studies, or retrospective studies using EMR databases are recommended for future research in order to obtain variables related to pregnancy history and specific gestational age, which are usually not available in claims databases, but essential in order to determine a woman's risk level of having a PTB. Thus, it is important to control for these covariates when evaluating the effectiveness of 17-OHPC in observational studies.

A universal approach to evaluate the adherence of 17-OHPC is needed to ensure the comparability of results from different studies. What is more, as mentioned in the above limitations section, home injections of 17-OHPC were not coded in the DRG database, which should be taken into consideration when assessing adherence in the future. The factors related to 17-OHPC utilization and adherence should also be explored further by qualitative studies or studies with mixed methodologies, since some factors or reasons cannot be obtained using currently available

databases.

Lastly, although the use of 17-OHPC was found to be associated with a lower incidence of hypertension (including GHT and preeclampsia), only a few of studies investigating this association were identified, and some of them were experiments on rats. Thus, whether 17-OHPC can be used as an option for preeclampsia treatment or prevention still needs to be investigated and confirmed by more studies in the future.

Appendix A

Figure A.1 Patient attrition process for Texas Medicaid databases

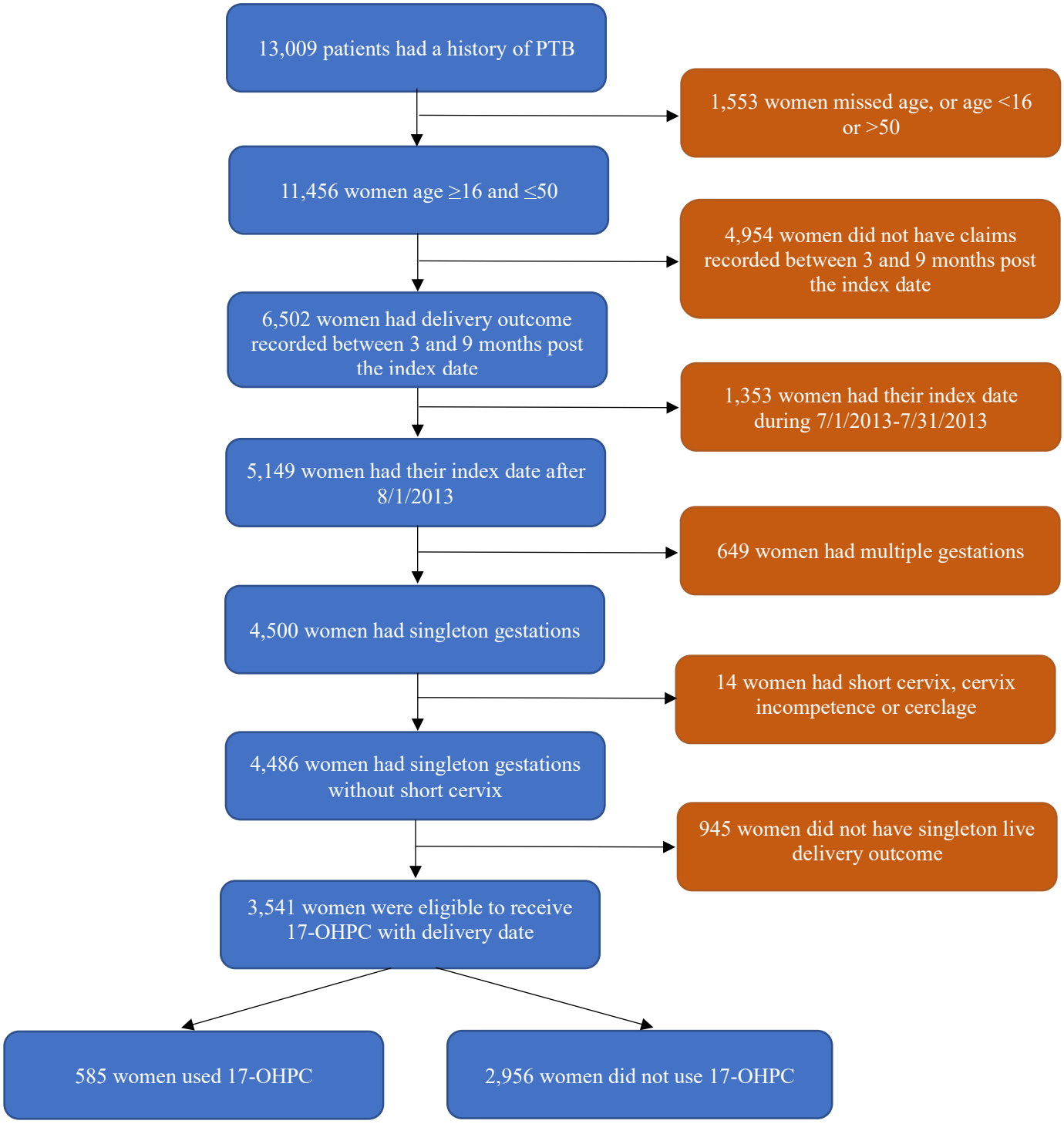


Table A. 1 Comparison of Age by Utilization Status of 17-OHPC in Texas Medicaid Databases

	Non-17-OHPC Users (N, %) N=2,956	17-OHPC Users (N, %) N=585	*p* Value[a]
Age group			0.39
16-24	1,261 (84.57)	230 (15.43)	
25-29	848 (83.30)	179 (16.70)	
30-34	622 (82.38)	133 (17.62)	
≥ 35	225 (81.23)	52 (18.77)	

[a] *p values were determined by cross-tabulations with chi square analysis, significant at p<0.05*

Table A. 2 Comparison of Race/Ethnicity by Utilization Status of 17-OHPC in Texas Medicaid Databases

	Non-17-OHPC Users (N, %) N=1,008	17-OHPC Users (N, %) N=227	*p* Value[a]
Race/Ethnicity			0.14
White	162 (83.94)	31 (16.06)	
Black	315 (84.00)	60 (16.00)	
Hispanic	531 (79.61)	136 (20.39)	

** Records of race/ethnicity were missing for 2,306(65.12%) patients*

[a] *p values were determined by cross-tabulations with chi square analysis, significant at p<0.05*

Table A. 3 Comparison of Age by Adherence of 17-OHPC in Texas Medicaid Databases

	17-OHPC Non-adherers (N, %) N=474	17-OHPC Adheres (N, %) N=111	*p* Value[a]
Age group			0.19
16-24	193 (83.91)	37 (16.09)	
25-29	135 (79.41)	35 (20.59)	
30-34	101 (75.94)	32 (24.06)	
≥ 35	45 (24.06)	7 (13.46)	

[a] *p values were determined by cross-tabulations with chi square analysis, significant at p<0.05*

Table A. 4 Comparison of Race/Ethnicity by Adherence of 17-OHPC in Texas Medicaid Databases

	17-OHPC Non-adherers (N, %) N=187	17-OHPC Adheres (N, %) N=40	*p* Value[a]
Race/Ethnicity			0.69
White	24 (77.42)	7 (22.58)	
Black	49 (81.67)	11 (18.33)	
Hispanic	114 (83.82)	22 (16.18)	

** Records of race/ethnicity were missing for 2,306(65.12%) patients*

[a] p values were determined by cross-tabulations with chi square analysis, significant at p<0.05

Table A. 5 Comparison of PTB Rate by Utilization and Adherence Status of 17-OHPC in Texas Medicaid Databases

PTB	Non-17-OHPC Users (N, %) N=2,956	Nonadherent 17-OHPC Users (N, %) N=474	Adherent 17-OHPC Users (N, %) N=111	*P* Value[a]
No	2,172 (73.48)	324 (68.35)	69 (62.16)	0.003
Yes	784 (26.52)	150 (31.65)	42 (37.84)	

[a] p values were determined by cross-tabulations with chi square analysis, significant at p<0.05

Table A. 6 Relationship Between 17-OHPC Utilization and Incidence of Diabetes or Hypertension in Texas Medicaid Databases

Maternal Complication	Non-17-OHPC Users (N, %) N=1,361	17-OHPC Users (N, %) N=249	*P* Value[a]
Diabetes[b]			0.70
No	1,313 (96.47)	239 (95.98)	
Yes	48 (3.53)	10 (4.02)	
Hypertension[c]			0.87
No	1,170 (85.97)	215 (86.35)	
Yes	191 (14.03)	34 (13.65)	

** Two months pre-index period was applied, so the sample size changed*

[a] p values were determined by cross-tabulations with chi square analysis, significant at p<0.05

[b] Gestational diabetes was included

[c] Gestational hypertension and preeclampsia were included

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